| Clinical Evaluation Report and Post-Market Clinical Follow-Up | Document No.：QD/QB-730-01-11 |
|---|---|
| | Version: A/0 |
| | Date: 2024-03-06 |

**PRODUCT:** Cooling Gel Sheet

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**REVIEWED BY:** Rong Cheng

**APPROVED BY:** Chen Ning

## 1. Purpose and Scope

According to the Regulation (EU) 2017/745, Article 61 and ANNEX XIV, the evaluation of the clinical performance and safety as well as the clinical benefit must be based on clinical data and is required for all medical device classes. The clinical evaluation report and the clinical data on which it is based, verifies the clinical safety and performance of the Cooling Gel Sheet.

A clinical evaluation plan [Risk Management Report] is in place and this clinical evaluation report is carried out in accordance with the plan.

## 2. Definitions

| Definition / Abbreviation | Description |
|---|---|
| MDR | Regulation (EU) 2017/745 |
| Certification | EN ISO 13485:2016 |

## 3. Product Information

| | |
|---|---|
| Manufacturer: | Foshan Biours Biosciences Co., Ltd. |
| Product name: | Cooling Gel Sheet |
| Product model: | BI-1-05 |
| CE marking: | CE Technical File |
| Classification: | Class A, Rule 1 |

### 3.1 Intended Use

For reducing fever and body temperature, relieving tiredness and sleepiness, and helping to prevent heatstroke during overheated days and nights.

### 3.2 Intended Users

Anyone suffering from a high body temperature or fever. However, when used on children or persons with disabilities, adult supervision is required.

### 3.3 Directions of Use

Cut or tear open pouch and remove the cooling gel sheet. Remove transparent film from the back of the cooling gel sheet and discard. Apply gel sheet surface on the affected area. The cooling gel sheet will not stick if the skin is wet. For the best results use each cooling gel sheet only once.

### 3.4 Operating Principle

Hydrogels are highly absorbent natural or synthetic polymers which can contain over 99.9% water. The polymer chains contain acidic or basic groups bound to them. The acidic groups on the chains deprotonate at high pH, whereas the basic groups protonate at low pH. In the presence of an aqueous solution, the polymer chains absorb water and the association, dissociation and binding of various ions to polymer chains causes the hydrogel to swell. As the temperature raises the heat of the skin causes the evaporation of water contained within cooling gel sheet which creates a cooling sensation on the surface of the skin.

## 4. Clinical Benefits

Through the polymer hydrogel with sodium polyacrylate as the base material, a large amount of purified water is loaded into the polymer gel. The heat generated by the human body when it has a fever is taken away by absorbing heat through the evaporation of water, thereby achieving the effect of cooling down and reducing fever, which has a physical cooling effect.

## 5. Clinical Claims

Cooling Gel Sheets have undergone necessary safety assessments from a clinical perspective. They are directly attached to human skin and have been identified in risk management documents. Cooling Gel Sheet products have been inspected in accordance with design requirements and are all qualified.

### 5.1 Risk Management Report

The risk management personnel have evaluated the risk evaluation/risk acceptability criteria set out in the company's risk management control procedures, and believes that the risk acceptability criteria based on risk management activities remain the original standard.

5.1.1 Severity level of damage

| Class Name | Code number | Qualitative description of severity |
|---|---|---|
| Lightness | S1 | Minor injury or no injury |
| Moderate | S2 | Medium damage |
| Fatal | S3 | One person dead or seriously injured |
| Catastrophic | S4 | Multiple deaths or serious injuries |

5.1.2 Probability rating of damage occurring

| Grade Name | Code number | Frequency (per year) |
|---|---|---|
| Very Few | P1 | The < 10 |
| Few | P2 | 10 -4 ~ 10 |
| A few | P3 | 10 -2 ~ 10 |
| Occasionally | P4 | 10 -1 ~ 10 |
| Sometimes | P5 | 1 ~ 10 |
| Often | P6 | > 1 |

5.1.3 Risk Assessment Criteria

| Probability | | Level of severity | | | |
|---|---|---|---|---|---|
| | | 4 | 3 | 2 | 1 |
| | | Catastrophic | Fatal | Medium | Light |
| Often | 6 | U | U | U | R |
| Sometimes | 5 | U | U | R | R |
| Occasionally | 4 | U | U | R | R |
| A few | 3 | R | R | R | A |
| Few | 2 | R | R | A | A |
| Very few | 1 | A | A | A | A |

# 6. Context of the Medical Device

## 6.1 Developmental Context

Since Foshan Biours Biosciences Co., Ltd., factory was established in 2011, we began to produce cooling gel sheets. We have more than 13 years' experience and export our cooling gel sheets to many countries around the world, such as: Italy, Croatia, Bosnia & Herzegovina, Montenegro, Saudi Arabia, Bahrain, Oman, Cambodia, Thailand, Malaysia, etc. We also sell our cooling gel sheets in the domestic market. The quality of our cooling gel sheet is very stable, as such we hardly receive any complaints.

### 6.2 State of the Art

This device technology originated from Japanese cataplasm technology and had a long history of application in Japan. For conventional technology. The clinical data used in the evaluation of this device were obtained from equivalent devices.

## 7. Clinical Evidence

From a clinical perspective, the cooling gel sheet has undergone the necessary safety assessment, and the cooling film product has been inspected and qualified according to the design requirements. The overall performance and specific characteristic data of this device are cooling performance, and the main function is cooling.

### 7.1 Clinical performance

A total of 57 patients of either sex, between 0-50 years of age were taken in which the diagnosis of pyrexia of primary origin (viral fever, infectious fever) was confirmed. Exclusion criteria: Patients with fever higher than 39°C and with acute complications were excluded from the trial. Pregnant and lactating women, patients with concomitant severe illness necessitating other medications, patients with severe hypertension, history of severe unstable angina, myocardial infarction, CVAs, renal failure, and those patients, who were not willing to give informed consent were also excluded from the study.

Table 1: Observations of the clinical trials

| Column Title | 0hr (A) | 1hr (B) | 2hr (C) | 4hr (D) | 6hr (E) | 8hr (F) |
|---|---|---|---|---|---|---|
| Mean | 2.589285 | 1.410714 | 0.660714 | 0.375 | 0.150943 | 0.132075 |
| Standard deviation (SD) | 0.4964 | 0.6260 | 0.8587 | 0.7523 | 0.5334 | 0.5203 |
| Sample size | 56 | 56 | 56 | 56 | 53 | 53 |
| Std. error of mean (SEM) | 0.06634 | 0.08365 | 0.1147 | 0.1005 | 0.07326 | 0.07146 |
| Lower 95% Conf. limit | 2.456 | 1.243 | 0.4306 | 0.1734 | 0.003803 | 0.2756 |
| Upper 95% Conf. limit | 2.722 | 1.578 | 0.8908 | 0.5766 | 0.2981 | 0.2756 |
| Minimum | 2.000 | 1.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Median ($50^{th}$ percentile) | 3.000 | 1.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Maximum | 3.000 | 3.000 | 3.000 | 3.000 | 3.000 | 3.000 |
| Normality test KS | 0.3852 | 0.4048 | 0.3149 | 0.4409 | 0.5171 | 0.5247 |
| Nornality test P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Passed normality test | No | No | No | No | No | No |

Table 2: Comparison table of the columns

| Comparison | Mean Difference | q | P value |
|---|---|---|---|
| Column A vs Column B | 1.179 | 13.630 | *** P<0.001 |
| Column A vs Column C | 1.929 | 22.304 | *** P<0.001 |
| Column A vs Column D | 2.214 | 25.609 | *** P<0.001 |
| Column A vs Column E | 2.438 | 27.809 | *** P<0.001 |
| Column A vs Column F | 2.457 | 28.024 | *** P<0.001 |
| Column B vs Column C | 0.7500 | 8.674 | *** P<0.001 |
| Column B vs Column D | 1.036 | 11.978 | *** P<0.001 |
| Column B vs Column E | 1.260 | 14.368 | *** P<0.001 |
| Column B vs Column F | 1.279 | 14.583 | *** P<0.001 |
| Column C vs Column D | 0.2857 | 3.304 | ns P>0.05 |
| Column C vs Column E | 0.5098 | 5.814 | *** P<0.001 |
| Column C vs Column F | 0.5286 | 6.029 | *** P<0.001 |
| Column D vs Column E | 0.2241 | 2.555 | ns P>0.05 |
| Column D vs Column F | 0.2429 | 2.771 | ns P>0.05 |
| Column E vs Column F | 0.01887 | 0.2123 | ns P>0.05 |

Primary efficacy parameters were considered as reduction in for body temperature and symptom score assessment. Secondary efficacy parameters were reduction in the incidence of adverse events and overall compliance to the therapy.

Statistical analysis was done on the basis of intent to treat, to compare the body temperature before and after every assessment. The minimum level of significance was fixed at 95% confidence limit and a 1-sided p value of <0.05 was considered as significant.

RESULTS AND DISCUSSION

Clinical Trails

About 73 patients were screened for trial out of them 57 patients gave complete follow up. There was significant difference observed in mean body temperature level from 2.589+/-0.496 to 0.132+/-0.520

The P value is < 0.0001, considered extremely significant. Variation among column is significantly greater than expected by chance.

Tukey-Kramer Multiple Comparisons Test

If the value of q is greater than 4.061 then the P value is less than 0.05.

No adverse events were noted during the treatment as therewere no significant changes observed in other symptoms.

The clinical trial of cooling gel sheets observed a significant difference in the body temperature and pyrexia pattern.

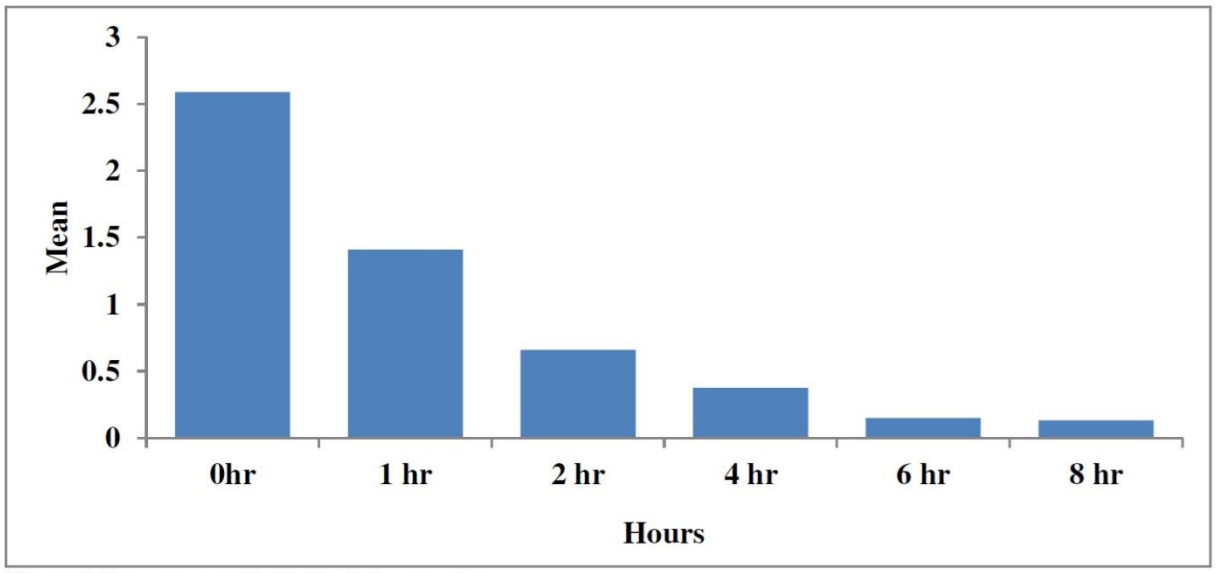


Figure 1: Improvement in the body temperature.

### 7.2 Systematic scientific literature review

| Item | Overseeing | Parameters | Results |
|---|---|---|---|
| Safety | Skin irritation | Negative or very slight reaction | Very slight reaction |
| | Formed tardive anaphylaxis | Negative | Negative |
| Characteristics | Initial adhesion | Should be able to adhere to No. 3 steel balls | Pass |
| | Stickiness | The sliding displacement should not exceed 1cm | Pass |
| | Heat resistance | Take it out after keeping it at 42℃±2℃ for 30 minutes. The gel should not flow. | Pass |
| | Cold resistance | Take it out after keeping it at -1℃±1℃ for 30 minutes. The gel should not freeze. | Pass |
| | Cooling performance | The temperature drop should not be less than 1℃ within 4 hours. | Pass |
| | Packing tightness | The packaging should be well sealed, with no continuous air bubbles leaking out, and no test water infiltrating. | Pass |

### 7.3 Clinical performance

The evaluation of the clinical data involves risks identified in risk management documentation. The conclusion is when the end-user is operating the device, safety and risks associated with the use of the device are acceptable, with respect to the intended use of the device.

## 8. Risk Management

A risk analysis, conducted in compliance with EN ISO 14971:2019 is currently documented in the:

- SOP Risk Management
- Risk Management Plan
- Risk Analysis
- Risk Management Report

### 8.1 Known Hazards and Risks

List hazards/ risks associated with the medical device.

| Level | Code | Probability of occurrence (per year) |
|---|---|---|
| Improbable | P1 | $<10^{-6}$ |
| Remote | P2 | $10^{-4}$~$10^{-6}$ |
| Occasional | P3 | $10^{-2}$~$10^{-4}$ |
| Probable | P4 | $10^{-1}$~$10^{-2}$ |
| Sometimes | P5 | 1~$10^{-1}$ |
| Frequent | P6 | >1 |

### 8.2 Known Side-Effects

None

### 8.3 Precautions and Warnings

- Do not apply it to wounds, mucous membranes, eczema and other skin injuries.
- Disposable external products, please do not reuse them.
- Please clean the application area and keep it dry before use to prevent sweat, hair, etc. from affecting the adhesiveness of the product.

- If skin discomfort occurs during use, stop using it immediately. In severe cases, please consult a physician.
- When used on children or persons with disabilities, adult supervision is required.
- This product is used to assist cooling of the body temperature when temperature is below 39°C. If the fever persists, and the body temperature is 39°C or higher, you should receive medical treatment.

### 8.4 Conclusion of Risk Management

Risk control measures were established and executed in accordance with the Risk Management Plan. These implemented measures are predominantly aligned with the adherence to relevant standards. Furthermore, technical control and monitoring measures were introduced and successfully validated for efficacy. The risk management process validates the adequacy of information materials provided by the manufacturer, ensuring that risk mitigation measures are accurately addressed in the Instructions for Use (IFU). Following the successful implementation of these risk control measures, both the remaining individual risks and the overall residual risks were evaluated as acceptable [Reference the Risk Management Report].

## 9. Post-Market Surveillance Data

Foshan Biours Biosciences Co., Ltd., has implemented a post-market surveillance (PMS) system to promptly identify new risks not previously recognized during the extended market experience. This commitment ensures the immediate execution of corrective and preventive actions, as detailed in reference to the post-market surveillance system. This section further consolidates insights gained from the medical device under evaluation and/or its equivalent devices, utilizing internal and external databases. The strategy for identifying pertinent reports is tailored to each database.

### 9.1 Recall Procedure

The company implements product recall procedures to comprehensively inspect the batch of products and trace the causes of product problems. Report to the general manager immediately; the general manager immediately presided over the recall team to hold a meeting in the conference room on the second floor on the morning of March 12, 2023.

1. Main content: Discuss the research business inspection application and batch delivery to the customer Shanxi Guangmingshu Biotechnology Co., Ltd., contract number 230214E-CN, and how to deal with functional problems found in some parts of the product during random inspection.
2. Discussion opinions: It is believed that product sampling inspection found that the release film of the product has been displaced, and the problematic product must be

recalled. The procedure: From the business sales order batch code - workshop finished product warehousing order batch code - warehousing outgoing order batch code - quality control raw material acceptance, inspection order batch code - procurement inspection task notice batch Code - Warehouse inventory product batch code to see if it is consistent with the company's products and determine the source of raw materials.

3. The basic information of this batch of products based on the batch, delivery customer, and contract number of the workshop finished product receipt is as follows: Customer Number: Shanxi Guangmingshu Biotechnology Co., Ltd. Product model name: Y-T3152-003; Specifications: 40×90mm; Order quantity: 32,500 pairs; Actual production quantity: 33082 pairs; Production workshop: workshop; Shift: / ; Production date: 2024-1-5; Inventory packaging identification is consistent with the identification of shipped products.
4. Check whether the batch code of the business is consistent with the batch of the product that the customer requested to return. After checking, the batch is consistent.
5. Check whether the finished product receipt form in the workshop is consistent with the inspection batch code 2024011 of the business. It is found that they belong to the same batch of products.
6. Check the warehouse's outbound order, the raw material acceptance record of quality control, and the batch of the purchased "inspection task notice" is consistent with the batch of the workshop and business; from this, it was found that the functional parameters of the inspected parts were unstable. Therefore, the batches of the products reviewed this time are consistent with the notification from Shanxi Guangmingshu Biotechnology Co., Ltd.
7. On March 11, 2023, the company business notified customers of Shanxi Guangmingshu Biotechnology Co., Ltd. that it is prohibited to sell this batch of products and all the products that have arrived will be shipped back at our expense.
8. 33082 pairs have been shipped, and there are 0 pairs in stock that have not yet been shipped.
9. On March 15, 2024, products that were found to have functional problems with some parts of the product during random inspections will be shipped back.
10. The products to be shipped back were sampled and tested under the supervision of the Inspection and Quarantine Bureau, and no abnormalities were found.
11. No abnormalities were detected after inspection, and the recall team decided to treat the returned products as scrap after research.

## 10. Benefit Risk Assessment

Providing an overviewing about risks and benefits for the medical device we conclude, why the probable benefits outweigh potential risks. The following list summarises an example of the evaluation of acceptability of the benefit-risk ratio. Based on the findings in the clinical data review as well as in the risk analysis, it can be inferred that the probability of a patient experiencing a substantial benefit when using the cooling gel sheet outweighs the probability of suffering harm due to a residual risk of the device significantly.

The cooling gel sheet risk management review team, after reviewing the products produced and the risk management process by checking the risk management documents, believes that:

- The risk management plan has been appropriately implemented.
- Appropriate methods are available to obtain relevant production and post-production information.
- The total residual risk is within the acceptable range of the risk acceptance criteria, and the benefits exceed the risks.

## 11. Summary & Conclusion

Since our factory was established in 2011, we thorough search within clinical experience databases (MHRA, BfArM, Swissmedic, and FDA) revealed no unevaluated risks or usability aspects, and residual risks are always deemed acceptable in the final risk management report, with the benefits outweighing these residual risks.

The clinical evaluation affirms compliance with relevant safety and performance requirements (Regulation (EU) 2017/745, ANNEX I, clauses 1 and 8). Overall, the clinical safety, performance, and benefits demonstrate that the cooling gel sheet aligns with current knowledge and technological standards.

Conclusions: The clinical evaluation confirms that the cooling gel sheet complies with current knowledge and technological standards, is suitable for its intended purpose and users, and offers substantial clinical benefits, outweighing potential adverse effects. Evaluated clinical data, aligned with Regulation (EU) 2017/745, are scientifically sound and comprehensive, supporting the device’s conformity. The analysis of literature, clinical data, and risk factors indicates that patient benefits significantly surpass the risk of residual harm, rendering further clinical investigations unnecessary.

A planned PMCF strategy, considering the clinical evaluation report’s results, defines the process and frequency of activities. In summary, the clinical safety, performance, and benefits showcased in this evaluation confirm that the cooling gel sheet adheres to relevant general safety and performance requirements (Regulation (EU) 2017/745, ANNEX I, clauses 1 and 8).

# Annex

## A1 References

The following table lists all relevant publications, provides a summary of the content and lists the appraisal.

| Serial Number | Risk assessment before acting | | Post-action risk assessment | | | Whether new risks arise | | Verify results |
|---|---|---|---|---|---|---|---|---|
| | Probability | Severity | Risk Level | Probability | Severity | Risk Level | Yes/No | Yes/invalid |
| H1 | S2 | P1 | A | S2 | P1 | A | No | invalid |
| H2 | S2 | P3 | R | S2 | P1 | A | No | invalid |
| H3 | S2 | P3 | R | S2 | P1 | A | No | invalid |
| H4 | S2 | P2 | A | S2 | P1 | A | No | invalid |
| H5 | S1 | P3 | A | S1 | P2 | A | No | invalid |
| H6 | S2 | P1 | A | S2 | P1 | A | No | invalid |
| H6 | S2 | P1 | A | S2 | P1 | A | No | invalid |

## A2 Selection of Literature Search Results

The following table lists all identified publications, the decision for potential relevance and final relevance.

| **Contents of the question** | **Characteristic judgment** | **Probable Harm** |
|---|---|---|
| C.2.1 What is the intended use of the medical device and how is the medical device used? | For reducing fever and body temperature. Cut or tear open pouch and remove the cooling gel sheet. Remove transparent film from the back of the sheet and discard. Apply gel sheet surface on the affected area. | None |
| C.2.2 Is the medical device intended to implant? | No | None |
| C.2.3 Is the medical device intended to come into contact with the patient or other person? | Yes, medical antipyretic patches in contact with the skin of the patients | Biological hazard |

| | | |
|---|---|---|
| C.2.4 What materials or components are used in, or in conjunction with, or in contact with medical devices? | Yes, the use of non-woven fabrics and polypropylene films in medical devices | Biological hazard |
| C.2.5 Is there energy given to or taken from the patient? | No | None |
| C.2.6 Was any substance provided to or extracted from the patient? | No | None |
| C.2.7 Does the medical device process biological material for subsequent reuse, infusion/blood, or transplantation? | No | None |
| C.2.8 Is the medical device provided in sterile form or intended to be sterilized by the user, or with other applicable microbiological control protocols? | No | Biological hazard |
| C.2.9 Is the medical device expected to be routinely cleaned and disinfected by the user? | No | None |
| C.2.10 Is the medical device expected to improve the patient's environment? | No | None |
| C.2.11Whether to Take a measurement? | No | None |
| C.2.12 Is the medical device analyzed? | No | None |
| C.2.13 Is the medical device intended to be used in combination with other medical devices, medicines or other medical technologies? | No | None |
| C.2.14 Is there an unwanted output of energy or matter? | No | None |

| | | |
|---|---|---|
| C.2.15 Are medical devices susceptible to environmental influences? | No | None |
| C.2.16 Do medical devices affect the environment? | No | None |
| C.2.17 Does the medical device have basic consumables or accessories? | No | None |
| C.2.18 Does it require maintenance and calibration? | No | None |
| C.2.19 Does the medical device contain software? | No | None |
| C.2.20 Is there a storage life limit for medical devices? | Yes, the shelf life is three years | Use hazard |
| C.2.21 Are there delayed or long-term use effects? | No | None |
| C.2.22 What mechanical forces do medical devices bear? | No | None |
| C.2.23 What determines the life of a medical device? | Moisture and gel adhesiveness | Hazards of use |
| C.2.24 Is the medical device intended for one-time use? | Yes | None |
| C.2.25 Does the medical device need to be safely removed from service or disposed of? | No | None |
| C.2.26 Does the installation or use of medical devices require specialized training or specialized skills? | No | None |
| C.2.27 How Do I Provide Safe Use Information? | Safe use information is detailed in the product manual | Information Hazards |
| C.2.28 Is it necessary to establish or introduce new manufacturing processes? | No | None |
| C.2.29 Successful use of medical devices. Is it critically dependent on human factors, e.g. user interface? | No | None |

| | | |
|---|---|---|
| C.2.29.1 Are User interface design features likely to cause usage errors? | No | None |
| C.2.29.2 Is the medical device used in an environment where it is used incorrectly due to distraction? | No | None |
| C.2.29.3 Does the medical device have connecting parts or accessories? | No | None |
| C.2.29.4 Does the medical device have a control interface? | No | None |
| C.2.29.5 Does the Medical Device Display Information? | No | None |
| C.2.29.6 Are medical devices Controlled by menus? | No | None |
| C.2.29.7 Is the medical device used by a person with special needs? | No | None |
| C.2.29.8 Can the User Interface be Used to initiate User actions? | No | None |
| C.2.30 Does the medical device use an alarm system? | No | None |
| C.2.31 In what ways may a medical device be intentionally misused? | Ingestion | Gastrointestinal hazards |
| C.2.32 Does the medical device hold critical data for patient care? | No | None |
| C.2.33 Is the medical device intended to be mobile or portable? | Yes, medical fever strips are portable | Hazard of use |
| C.2.34 Does the use of medical devices depend on basic performance? | No | None |

## A4 Qualification of Authors

### **AUTHOR:** He Jian Qiang

Qualification and experience: He Jian Qiang university majored in biotechnology and graduated in June 2015. He has been working at Foshan Biours Biosciences Co., Ltd., for 7 years. He Jianqiang is Rong Cheng's assistant, and he is technical staff in Biours, mainly responsible for assisting Rong Cheng in writing technical documents and creating product formulas.

### **REVIEWED BY:** Rong Cheng

Qualification and experience: Rong Cheng University majored in pharmaceutical engineering and graduated in June 2012. She has been working at Foshan Biours Biosciences Co., Ltd., for 12 years. She is a technical Supervisor in Biours, many of the company's technical documents were written and provided by her, and the product formulas are tested, debugged and produced by her.

### **APPROVED BY:** Chen Ning

Qualification and experience: Chen Ning university majored in chemical-industry and graduated in July 1990. He has been working at Foshan Biours Biosciences Co., Ltd., for 10 years. Before coming to Biours, he had been working in the chemical industry and had plenty of experience. He is the person in charge of the Biours factory. Factory all documents and procedures need to be decided and implemented by him.