Introduction of test for Particulate Contamination: Sub-visible Particles in ChP

CHEN Guiliang

Shanghai Center for Drug Evaluation and Inspection

ICH Q4

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Source of Sub-visible Particles

- The sub-visible particles are mainly composed of inorganic particles such as calcium and silicon, or carbon black, fiber, bacteria, mould, spore and crystal, glass debris, plastic particle, rubber particle and the other substances. Main sources:
- **(1) Pollution in drug manufacturing, storage, transportation and clinical dispensing operation;**
  - Particles from the manufacturing environment and the liquid. Even though the liquid has undergone a filtration step before filling, it is impossible to remove all the particles, and a small amount of particles remain.
  - Particles from the packaging containers such as glass ampoules. Even though the ampoules are washed before they are used, some particles are still inevitably left.
- **(2) Physical or chemical changes during drug storage and drug compatibility.**
  - The composition of glass is mainly composed of silica, with addition of some oxides (such as B2O3, Al2O3, CaO, MgO, BaO, K2O and Na2O) for mixing and melting. During storage of injection, silica and these oxides in the glass may react with the components of the injection to form sub-visible particles .
  - Drug incompatibility.

Hazards of Sub-visible Particles

- Particles entering the blood vessels can cause vascular occlusion, granuloma, phlebitis and thrombosis and cause damage to the heart muscle and other organs (such as liver and kidney);
- Cause an allogeneic reaction;
- Ensure that the intrinsic quality of the injection can meet GMP requirements.

Cause of the Adverse Reactions of Traditional Chinese Medicine Injections: Sub-visible Particles

- Sub-visible particles are one of the leading causes of adverse reactions of traditional Chinese medicine injections;
- Inappropriate choice of vehicle causes the amount of sub-visible particles to be out of specification: most of the traditional Chinese medicine injections contain organic macromolecule compounds such as gelatinous pigments and proteins. The change of pH and the action of ions in the vehicle will cause an increase in the amount of sub-visible particles in the solution;
- Inappropriate drug compatibility causes the number of sub-visible particles to be out of specification: Perhexiline injection is extracted and processed from the two herbs of Danshen and Ligusticum wallichii, and is made up of polysorbate 80, disodium edetate and sodium hydrogen sulfite. Therefore, when it is compatible with other drugs, the diversity and complexity of chemical changes also increase, and the color change of the drug solution, the increase of sub-visible particles and turbidity often occur;
- Improper operation of the drug solution preparation causes the amount of sub-visible particles to be out of specification;

Liu Wenqing, Wang Yue, Du Shouying, and Xiao Yao: Beijing University of Chinese Medicine

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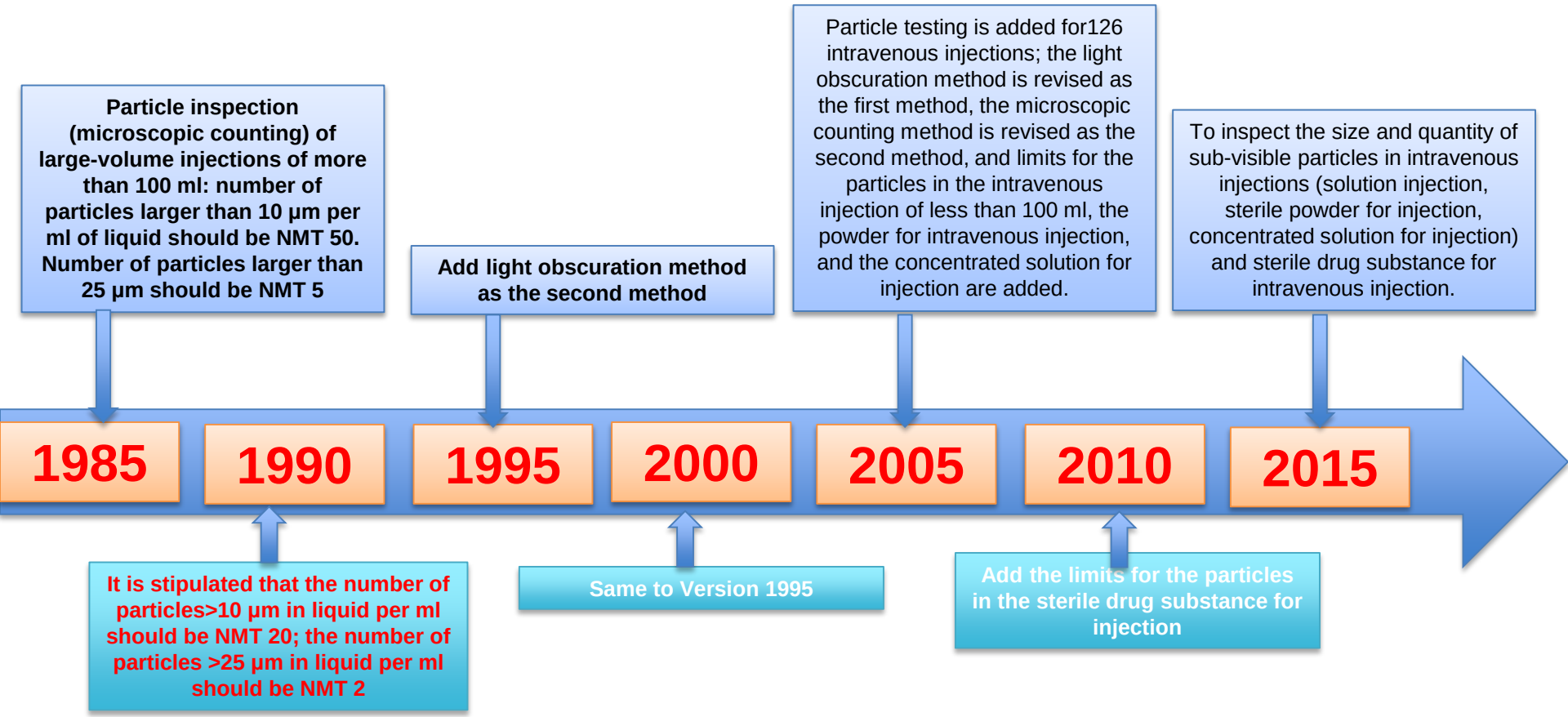
History of Listing Test for Sub-visible Particles



Inspection Methods and General Requirements

- Light obscuration method - The light obscuration method is not suitable for preparations with high viscosity and preparations that are easy for crystal precipitation, and is not suitable for injections that are prone to bubbles when entering the sensor.
- Microscopic counting method - When the result of light obscuration method does not meet the requirements or the test sample is not suitable for the determination by light obscuration method, it should be measured by microscopic counting method, and the results of microscopic counting method should be used as the basis for determination.
- For the injection with high viscosity which cannot be directly measured by both methods, dilution with suitable solvent can be conducted before determination.

Test Environment and Testing

- Foreign particles should not be introduced into the test operating environment, and the operation before the determination should be carried out on a clean bench. Glassware instrument and other required supplies should be clean and free of particles.
- The water for particle inspection (or other suitable solvent) used in this method should be filtered through a microporous membrane of not more than 1.0 μm before use.
- The water for particle inspection(or other suitable solvent) meets the following requirements: (1) The light obscuration method takes 50 ml for determination and the number of sub-visible particles of 10 μm or more per 10 ml should be less than 10, and the number of sub-visible particles of 25 μm or more should be less than 2. (2) The microscopic counting method takes 50 ml for determination and the number of sub-visible particles of10 μm or more should be NMT 20, and the number of sub-visible particles of 25 μm or more should be NMT 5.

General Requirements for the Instrument

- The instrument usually includes three parts namely sampler, sensor and data processor.
- The measured particle diameter ranges from 2 to 100 μm, and the detected particle concentration is from 0 to 10,000 /ml.
- The instrument used should be calibrated at least every 6 months.

(1) Sampling volume

(2) Particle counting

(3) Sensor

(4) Self-test can be performed if the instrument used has a self-test function

- **Instruments usually include clean benches, microscopes, microporous membranes and filters, and plates.**
- **In clean bench, the high-efficiency air filter has a hole diameter of 0.45 μm and the air flow direction is from inside to outside.**
- **Microscope: Binocular large-field microscope with a micrometer (5 to 10 μm per cell) attached to the eyepiece. The front and rear movement range of the coordinate axis should be greater than 30mm. The microscope device is equipped with illumination devices with adjustable light projection angle and light intensity. It can be magnified 100 times during detection.**
- **Microporous membrane: pore size is 0.45μm, diameter is 25mm or 13mm, one side is printed with a grid with 3mm spacing; if there are sub-visible particles of 10μm or more on the membrane, the number should be NMT 5, and there should be no particles of 25μm or more. If necessary, the particles can be flushed with water for particle inspection in order to meet the requirements. (black or gray?)**
- **Preparation before inspection**

Testing Method

- (1) Intravenous injection or concentrated solution for injection with labeled volume of 25 ml or more
- (2) Intravenous injection or concentrated solution for injection with labeled volume of less than 25 ml
- (3) Sterile powder for intravenous injection
- (4) Sterile API for injection: According to the requirement of each preparation, take the appropriate amount of the test sample (equivalent to the maximum strength of each preparation)

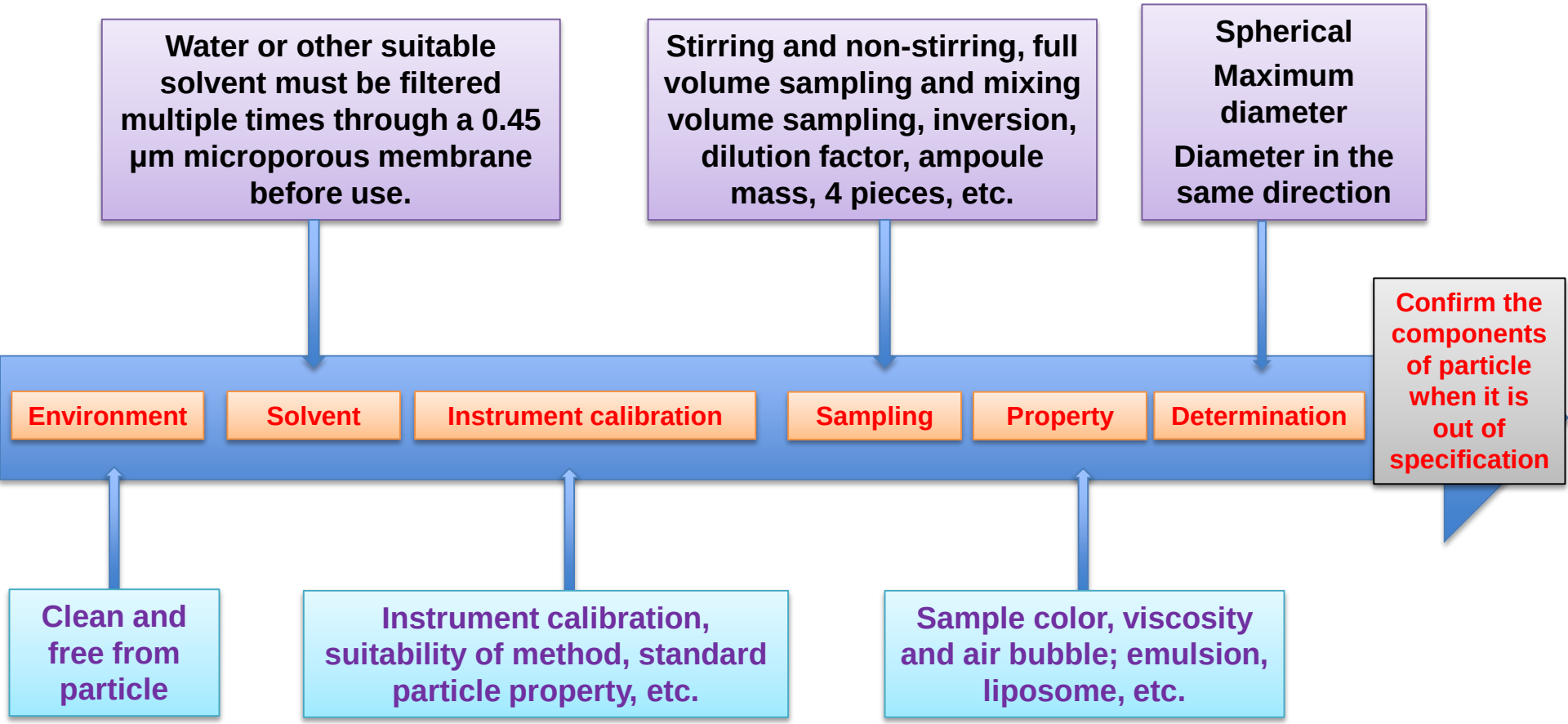
- **(1) Intravenous injection or concentrated solution for injection with labeled volume of 25 ml or more**
- **(2) Intravenous injection or concentrated solution for injection with labeled volume of less than 25 ml**
- **Sterile powder for intravenous injection and sterile API for injection. Unless otherwise specified, the test solution is prepared according to the inspection method (3) or (4) of the light obscuration method, and is determined by the above (1) procedure.**

Result Determination

- (1) For intravenous injection with labeled volume of 100ml or more, unless otherwise specified herein, the number of particles of 10 μm or more per 1ml should be NMT 25; the number of particles of 25 μm or more per 1ml should be NMT 3.
- (2) For intravenous injection with labeled volume of less than 100 ml, sterile powder for intravenous injection, concentrated solution for injection, and sterile API for injection, unless otherwise specified, the number of particles of 10 μm or more in each test container (part) should be NMT 6000, and the number of particles of 25 μm or more should be NMT 600.

- **(1) For intravenous injection with labeled volume of 100ml or more, unless otherwise specified herein, the number of particles of 10 μm or more per 1ml should be NMT 12; the number of particles of 25 μm or more per 1ml should be NMT 2.**
- **(2) For intravenous injection with labeled volume of less than 100 ml, sterile powder for intravenous injection, concentrated solution for injection, and sterile API for injection, unless otherwise specified, the number of particles of 10 μm or more in each test container (part) should be NMT 3000, and the number of particles of 25 μm or more should be NMT 300.**

Operation Factors Affecting the Test Results



Sub-visible Particles in the Prefilled Injection Syringe Assembly

- 6 batches of prefilled injection syringe samples of different specifications from 2 manufacturers are randomly selected, and the sub-visible particles in **water** are determined by light obscuration method, and the values are large or even out of specification;
- When a mixture of **water and isopropanol** (volume ratio = 1:1) is used as a solvent for the particle inspection of the assembly, it is apparent that oily droplets are present on the surface of the mixed solution, and the oily droplets are **silicone oil**;
- Isopropanol is used as a solvent for particle inspection of the assembly. It can be determined that the number of sub-visible particles in the assembly is not affected by silicone oil, which is consistent with the results of the microscopic method.

Wang Dongwei, Dong Dandan, Qian Chengyu: Jinan Pharmaceutical Packaging Material Testing Center of the China Food and Drug Administration

Control of Particles during Manufacturing Process

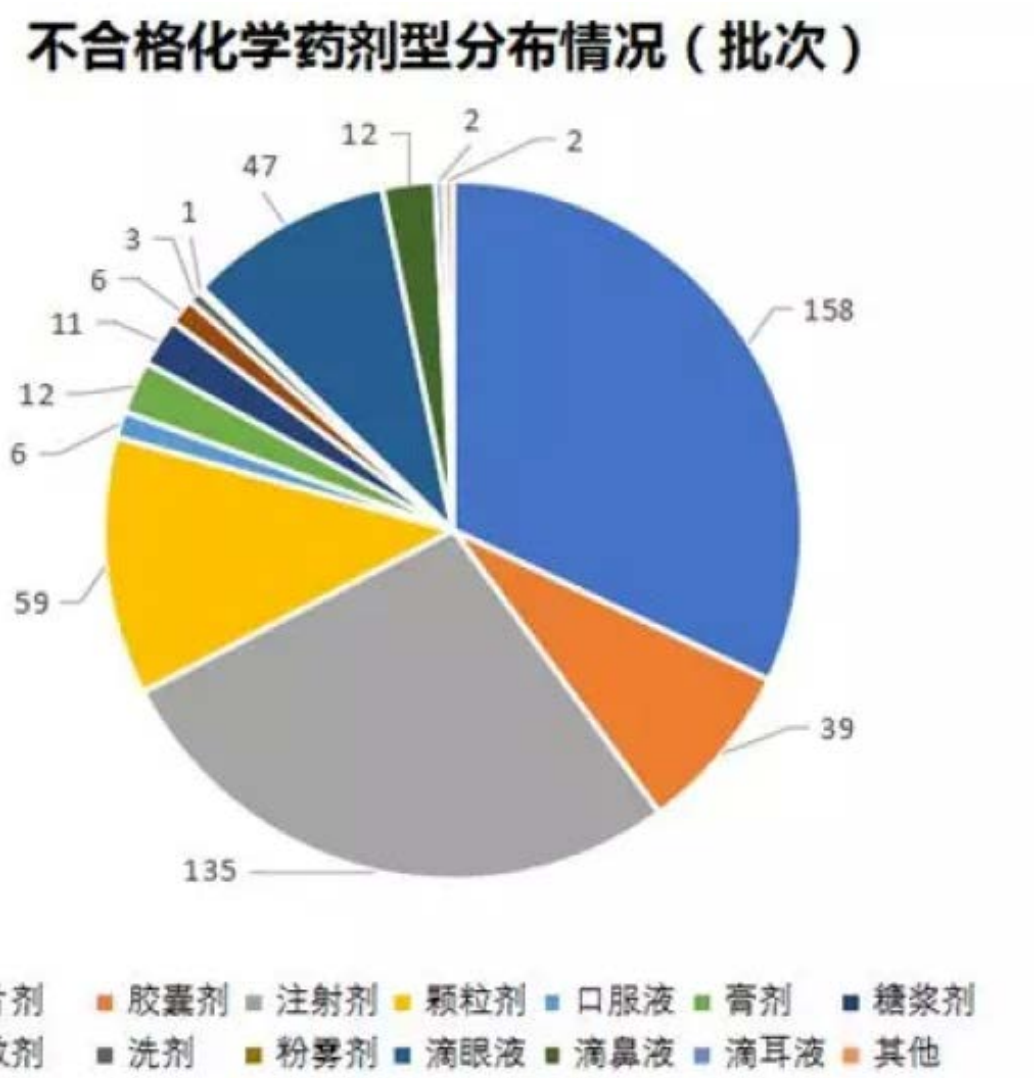
There are many kinds of particles in the injection, some of which are from raw materials, excipients and packaging materials; some are produced from the manufacturing process of injection; some are produced during use. In general, the main reasons for generation of particles are:

- **Due to the large amount of impurities in the raw materials and excipients, particles are formed during the heating process.**
- **The prescription has defects, which acts on the packaging material or excipients to form particles;**
- **The cleaning of the manufacturing environment does not meet the requirements, and the dust particles in the air form tiny particles falling in the liquid to form particles.**
- **Fibers of the filter material used in the manufacturing process form the fibrous particles.**
- **The packaging container dissolves particles due to washing and high temperature sterilization.**
- **Particles are introduced by the infusion equipment and needle rubber stopper during the use of injection.**

Control of Particles during Use Process

- Establish an PIVAS center: The hospital's good dosing environment, i.e. the establishment of PIVAS center, especially the pediatric PIVAS center, is very beneficial for reducing particulate contamination during dosing;
- Promote the application of new technology products: double-valve stand-up bag and double-tube non-PVC soft bag are large-capacity injection products in fully enclosed packaging, which can be self-shrinking without air intake during clinical use, thus completely eliminating the secondary air pollution in the hospital. Plastic ampoule injection produced significantly less particles than that of glass ampoule injection. At the same time, it can be opened by torque, which is easy to operate; it will not scratch the medical staff; the material is strong, good resistance to collision and easy to transport and carry.
- Selection of intravenous finished products to reduce dosing: In clinical applications, large-volume intravenous injections are often used in combination with small-volume injections. At this time, particles are introduced or produced. The number of particles detected after injection dosing is significantly higher than the number of particles before dosing. The Pharmacopoeia does not limit the sub-visible particles of the mixed solution after compatibility;
- Use precision infusion filter: In order to fully filter the particles in the mixed solution after dosing, the use of infusion apparatus with a precision filter will improve the safety and effectiveness of the infusion.

Annual Analysis Report on Out of Specification Drug Data for the Year of 2017



Ribostamycin Sulfate Injection

- The particle size, particle shape and particle diameter distribution of the product are investigated by image particle size and shape analyzer, and the correlation analysis is made on the number of sub-visible particles , which shows a positive correlation. **Due to the manufacturing process problem**, the particle size distribution of the products of different batches varies greatly, which increases the incidence of adverse reactions of the product. (?)
- Encouragement and hope.

Conclusion

- **Control of sub-visible particles and improvement of drug quality**
- **Correct selection of measurement methods and control of the test environment**
- **Development of Standard Operating Procedures**
- **Supplement to Various Testing Methods - Visible Particle and Electrical Resistance Method**
- **Progress (Different Granularity Requirements)**

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