

Quality Assurance For Antimicrobial Devices

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Quality assurance (QA) of products with antimicrobial claims is still a virgin field for medical devices. As the market pushes the development of new devices with antimicrobial properties there is rapidly growing interest on antimicrobial testing. QA systems for antimicrobial device testing are discussed here.

Current situation

Drug-resistant pathogens are a growing threat to people, particularly in health-care settings. Each year approximately 2 million patients in the United States (US) get infected by nosocomial microorganisms; of these, approximately 9000 die as a result of their infection.¹ More than 70% of the bacteria that cause hos-

pital-acquired infections are resistant to at least one of the drugs most commonly used to treat them and this tendency is increasing.² One major source of nosocomial infections are medical devices commonly used in hospitals and health care. Recent reports of strains resistant to vancomycin, which has been deemed to be the drug of “last resort” when treatments with other antibiotics have failed, emphasise the need for antimicrobial-equipped medical devices. The demands on those new devices are complex (Table I). The product should display a broad antimicrobial activity against various microorganisms without affecting patients’ health. In addition, the antimicrobial additive should not interfere with physiochemical and mechanical properties of the treated material and must be applicable to existing formulations and manufacturing processes. Furthermore and most importantly, the integration of new antimicrobial properties in products must ultimately be economical. Today, a variety of antimicrobial active additives is available on the market. Table II gives an overview of the major antimicrobial compounds used as additives for materials for medical devices.

claim higher security, reduced rates of infections and better performance, the antimicrobial efficiency of the product is not apparently visible to the user. Therefore, an objective assessment of these antimicrobial properties is of fundamental interest for all stakeholders, manufacturers, users and regulatory authorities. Because medical technology is a multidisciplinary and thematically wide field of research and application, testing of new device properties becomes a complex task. For the development, production and regulatory issues of new antimicrobial devices, quality assurance (QA) is a critical prerequisite. The users of the products expect better quality and fewer infections, regulatory authorities require a validated surveillance of production and performance, and health insurance companies seek a reduction of costs for the respective diagnose-related groups. Although the expectations differ between these groups, an appropriate QA system to guarantee the antimicrobial performance of the final product can satisfy all of them. Furthermore, certified QA systems are increasingly important to strengthen a company’s position in the competitive market.

An internationally standardised definition of the term “antimicrobial” is still lacking. So far, an antimicrobial

Table I: Characteristics demanded of new antimicrobial products and technology solutions.

- Broad effectiveness as antimicrobial
- Nontoxic or low toxic effects
- Long lasting efficacy
- Suitable formulations for specific manufacturing processes
- Appropriate economics

Table II: Major antimicrobial additives in biomaterials.

- Antibiotics
- Chitosan
- Coagulants
- Metals such as silver and their compounds
- Titanium dioxide
- Triclosan
- Organic biocides
- Quaternary ammonium compounds

New antimicrobial products

Although antimicrobial products

agent has been defined as a substance that inhibits growth or multiplication of microorganisms, or kills them.³ However, which microorganisms and to what extent is still unclear and not defined. A level of germ reduction by 99% of the initial load is commonly used for purposes of defining antimicrobial product features. Thus, a testing system that is able to assess slight differences in antimicrobial behaviour of those next-generation products would break new ground.

Requirements for QA

Like all medical products, antimicrobial devices cannot escape the challenges of QA on the features that they are deemed to possess. Therefore, a sensitive and reproducible monitoring system is required for reliable detection of variations in a production process. The nature and extent of the measurements needed is dependent on the final product and its antimicrobial claims and must be defined individually for each product. In addition, profitability is a fundamental aspect. Depending on the batch size and sales figures cost-effective QA becomes a critical parameter. Strong antimicrobial claims substantiated by an appropriate QA system provide an improved market position and thereby competitive advantages.

A reliable testing technology used for QA must fulfil diverse criteria. Ideally, the testing method should be able to simulate product-specific conditions, for example, the antimicrobial behaviour of catheters in blood or urine. The test method must be adaptable to a variety of different microorganisms to allow testing of product- and application-relevant germs to substantiate the claimed antimicrobial properties. The testing technology must substantiate antimicrobial efficacy in daily use. In addition, high throughput testing that can be automated results in higher reproducibility, precision and saving economy of time and human resources, thereby, also enabling QA of large batches with high sampling rate.

Validation of a test method also plays an important role during research and development as well as for QA. The implementation of validated measurement systems into QA as part of the production routine permits continuous surveillance of product quality. This becomes more important as the production process becomes more complex, for example, homogenous compounding or surface coating of the antimicrobial agent. Here, a potent QA system would be able to detect local defects

that ultimately lead to diminished antimicrobial performance of the whole product. This is of particular importance because stronger claims on antimicrobial performance may in future demand that antimicrobial features are permanently controlled in a lot-specific manner. Thus, an accredited test method with acceptance by authorities facilitates regulatory approval of new products. Outsourcing QA testing to external laboratories will provide objectivity and independence and in some cases save time and cost. However, in all cases, a validated QA system contributes tremendously to the credibility and reliability of the antimicrobial product and can therefore add to user confidence.

Antimicrobial testing methods

Some conventional screening systems and their derivatives have been available for years, but their usability and versatility is mostly unsuitable for QA aspects. Therefore, a powerful testing method is needed to monitor the performance of antimicrobial products. Table III gives a short summary of the most common testing methods and their advantages and limitations for antimicrobial QA.

Widely used is the agar diffusion assay and comparable methods

Table III: Advantages and limitations of antimicrobial testing methods.

Testing method	Advantages	Limitations
Agar diffusion	<ul style="list-style-type: none"> ■ Easy handling 	<ul style="list-style-type: none"> ■ Suitable only for release systems
JIS Z 2801:2000	<ul style="list-style-type: none"> ■ Japanese industry standard ■ Testing of product-specific conditions and relevant germs 	<ul style="list-style-type: none"> ■ Sizable variations ■ Unsuitable to measure water-repellent surfaces
AATCC-100	<ul style="list-style-type: none"> ■ US textile standard ■ Testing of product-specific conditions and relevant germs 	<ul style="list-style-type: none"> ■ Sizable variations ■ Unsuitable to measure water-repellent surfaces
ASTM E2801	<ul style="list-style-type: none"> ■ US testing and material standard ■ Testing of relevant germs 	<ul style="list-style-type: none"> ■ Sizable variations ■ Unsuitable to simulate product-specific conditions
Novel test method	<ul style="list-style-type: none"> ■ Testing of product-specific conditions and relevant germs ■ Can test many specimens ■ Automation ■ High throughput ■ Parallelisation, standardisation ■ FDA Device Master File ■ Fits the needs of ISO 17025 for testing medical devices 	<ul style="list-style-type: none"> ■ Small test specimens

that are based on the inhibition of microbial growth by the release of a diffusible antimicrobial agent into an agar medium that contains the microorganisms. The appearance and size of a zone of inhibition surrounding the test sample is indicative of antimicrobial activity. The main limitation of these assays is that only the performance of systems that release antimicrobials into the surrounding environment can be tested, but not systems with only surface-active additives. Those release systems are not suitable for the medical device or packaging industries, because release of antimicrobial additives is unwanted or even forbidden. These types of material may be classified by registration authorities as drug release systems rather than medical devices and, thus, may fall under drug registration laws.

Another kind of assay is based on the incubation of test samples with microbes of known cell count. After incubation, the specimens are washed and the adherent cells are then removed and plated out on agar plates

for colony forming unit counting. Microbial reduction is then calculated in relation to a control sample. Several variants of this testing have been introduced. Amongst these are the Japanese Industry Standard (JIS Z 2801:2000)⁴ and the Standard of the American Association of Textile Chemists and Colorists (AATCC-100).⁵ In the American Society for Testing and Materials (ASTM)⁶ E2801 testing standard the antimicrobial activity of samples is measured in agar slurry that contains the microbes. However, all testing methods are labour-intensive in handling with variable reproducibility and low precision. Other shortcomings of these assays include the requirement of high sample numbers for statistical significance and high cost. Poor standardisation and automation also limit the applicability of these tests for QA purposes.

A novel proliferation assay has been developed based on the release of vital daughter cells from the surface of a device into its surroundings. The proliferation activity of these daughter cells, which are responsible for infection development, can be monitored in a time course. Antimicrobial activity is monitored by the time needed to reach a defined optical density, which is dependent on the number of released daughter cells (Figure 1).⁷ In comparison with an untreated control (lane 1), increasing concentrations of an antimicrobial additive in a polymer (lanes 2–5) clearly result in delayed (shift to the right) or even inhibited growth (flat line). This testing technology enables a broad spectrum of conditions and different germs to be tested. Simultaneous measurement of 8-fold replicates provides improved standardisation and reproducibility. Furthermore, the proliferation assay allows the parallelised measurement of multiple samples under unified and standardised conditions. In addition, automation and throughput of 80 test samples and 16 internal controls per microtiter plate allow the integration of this technology in QA. Testing laboratories have been

accredited with this method and recently a Device Master File for this test method was submitted to the US Food and Drug Administration. One point to note with this test is that small testing specimens have to be provided (3-mm width and 7-mm length), because testing is performed in a 96-well plate.

Future focus

The medical device market is highly competitive and innovative. New technologies and higher prices must be justified to support the medical benefits of their use. In this context the implementation of validated QA systems becomes a crucial competitive instrument. Thus, reliable QA testing systems in manufacturing and product control are essential elements for success in the market and will tremendously contribute to the credibility and reliability of antimicrobial products and the companies that produce them. The introduction of the novel test described here helps in this regard because it provides the quantitative features required of modern analytical systems and useful quantification of antibacterial efficacy.

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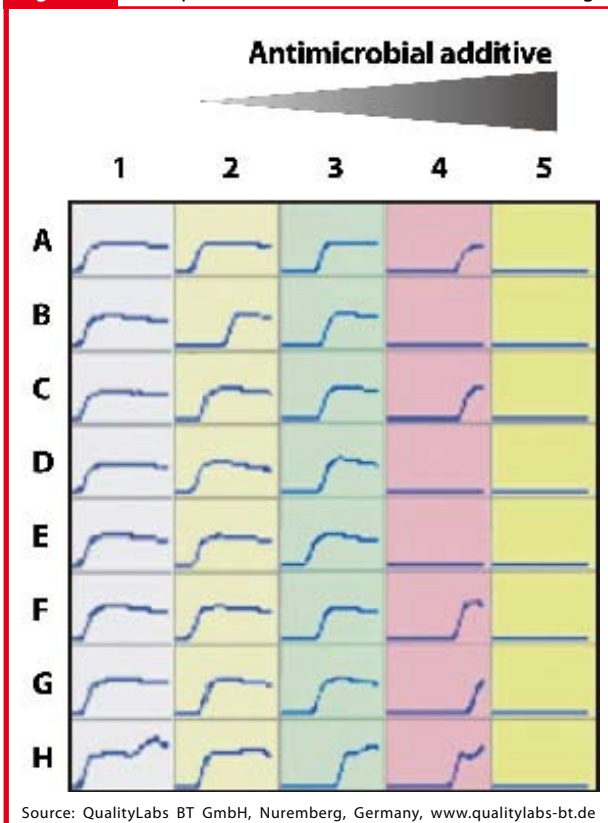
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Fig 1: Example results of novel antimicrobial testing.



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