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CARDIOVASCULAR MEDICAL DEVICES: REGULATORY SCIENCE RESEARCH OVERVIEW IN THE OFFICE OF SCIENCE AND ENGINEERING LABORATORIES (OSEL) AT THE FOOD AND DRUG ADMINISTRATION (FDA)

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ABSTRACT

The Cardiovascular Research Program in OSEL at the FDA consists of a diverse group of engineers and scientists who seek to drive innovation in cardiovascular device technology through development and standardization of pre-clinical test methods using in vitro, in vivo, and in silico models. The goal is to improve the pre- and post-market regulatory review processes and to accelerate patient access to safe and effective cardiovascular medical devices (e.g., heart valves, ventricular assist devices, cardiopulmonary bypass and cardiac mapping systems, ablation catheters, pacemakers, defibrillators, cardiac occluders, etc).

Keywords: FDA, OSEL, Cardiovascular, Hemocompatibility, Hemodynamics, Device Durability, Electrophysiology.

1. INTRODUCTION

The Cardiovascular Research Program at OSEL (https://www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories) currently focuses on four different regulatory science research areas for cardiovascular medical devices: ***Hemocompatibility, Hemodynamics, Device Durability, and Electrophysiology***.

(1) **Hemocompatibility** research group develops *in vitro*- and *in silico*-based pre-clinical blood damage assessment tests for hemolysis and thrombosis. (2) **Hemodynamics** research group develops pre-clinical test methods and validated computational models to assess hemodynamic performance using simulated pathophysiological conditions. (3) **Device Durability** research group evaluates mechanical fatigue, corrosion, and mechanically-assisted material degradation to assess acceptable device performance through the lifetime of devices. (4) **Electrophysiology** research group develops *in vitro* and *in silico* assessment methods for improving safety and effectiveness of electrophysiology devices.

2. MATERIALS AND METHODS

Examples of completed, ongoing, and future research projects from each of the four research groups mentioned above are presented and discussed below:

2.1 Hemocompatibility Research Group

Adverse patient events related to blood damage remain a major clinical concern and often contribute to patient morbidity and mortality. Preclinical hemocompatibility evaluations of blood-contacting medical devices and biomaterials are important in preventing these devices from causing excessive damage to red blood cells (hemolysis), increased bleeding, platelet activation, and blood clot formation (thrombosis). However, the lack of standardized testing and well-established pass/fail criteria for acceptable levels of blood damage during *in vitro* testing with animal blood makes it difficult for the FDA and industry to know how bench testing results correlate to real-world performance in patients. Moreover, current premarket thrombosis testing approaches rely heavily on animal studies, which are very resource-demanding, and sometimes produce questionable data due to confounding factors and inherent limitations of the animal models. To enhance patient safety, a combination of *in vitro*, *in silico*, and *in vivo* tools are needed to appropriately assess the

hemocompatibility potentials of various blood-contacting devices in a least burdensome manner. The aim of this research thrust is to improve pre-clinical blood damage assessments by developing, refining, validating, and standardizing robust *in vitro* and *in silico* test methods to screen medical devices and materials, to better predict clinical outcomes, and to facilitate device innovation.

To improve test methods and reduce the use of *in vivo* animal studies, the group developed dynamic *in vitro* test loop systems (Fig. 1a) to evaluate the thrombogenicity potential of medical devices and biomaterials under dynamic blood flow conditions. To compensate for blood coagulation differences between donors and species, a new static material pretest (Fig. 1b) was also developed to determine donor-specific anticoagulation levels [1]. Biomarkers based on platelet count, percent thrombus surface area coverage, and thrombus weight showed that the positive control latex material had the most thrombogenic response (Fig. 2), while PVC and silicone exhibited a moderate thrombogenic response that was greater than the other commonly used device materials (e.g., PTFE, HDPE, Poly-urethane [PU]) tested in the flow loop. The results demonstrate that the dynamic flow test loop system is a useful tool to effectively differentiate materials with different thrombogenic potentials.

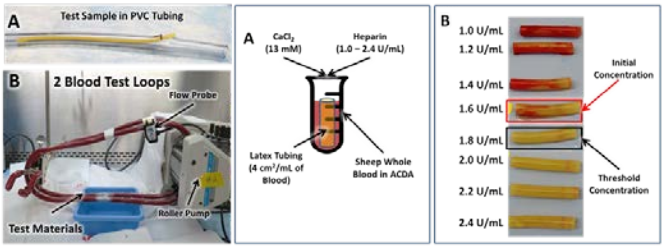

FIGURE 1a (left) AND 1b (right): (1a) A – TEST MATERIAL INSERTED INTO PVC TUBING, B – TWO DYNAMIC FLOW TEST LOOPS. **(1b)** A – STATIC MATERIAL PRETEST PROTOCOL, B – RESULTS FROM DONOR-SPECIFIC BLOOD COAGULABILITY TEST TO DETERMINE TARGET HEPARIN CONCENTRATION (U/mL) FOR DYNAMIC FLOW LOOP TESTING.

One of the critical evaluations of a fully-functioning medical device is an *in vitro* dynamic hemolysis test under simulated clinical use conditions. Due to the lack of an absolute pass/fail hemolysis acceptance criterion and variability between blood sources, current device safety assessments are usually based on paired comparisons of hemolysis caused by a new device concurrently tested against a clinically-used comparator device. However, this practice is limited if an appropriate comparator device is not available, or the new device causes more hemolysis than the comparator but may still be safe for its intended clinical application. To improve device design evaluation and regulatory review, FDA is creating tools for determining acceptable levels of *in vitro* and *in vivo* hemolysis for different patients and device applications (e.g., adult and pediatric patients exposed to cardiopulmonary bypass devices, hemodialysis, short-term blood pumps, VADs, rapid infusion pumps). This is being accomplished through *in vitro* testing to relate levels of hemolysis between animal and human blood in different flow models, data mining FDA device submissions to establish typical *in vitro* hemolysis values for blood pumps, and developing a biokinetic model for predicting adverse patient events based on plasma hemoglobin toxicity using animal and clinical data [2].

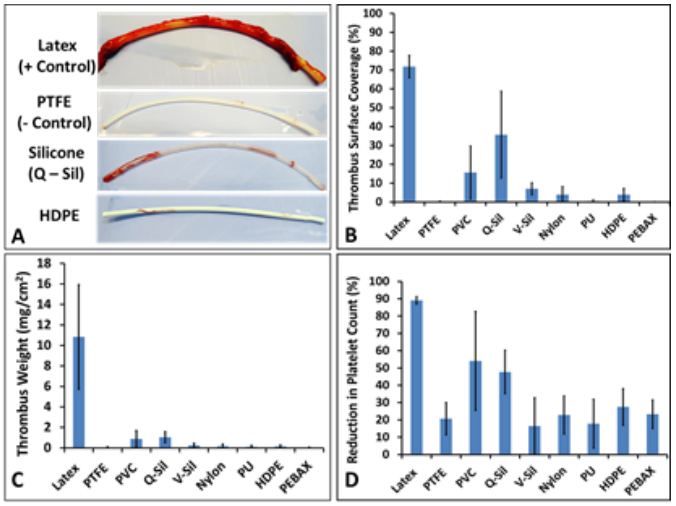

FIGURE 2: (A) REPRESENTATIVE IMAGES OF THROMBUS DEPOSITION ON THE SELECTED TEST MATERIALS; (B) THE EFFECT OF MATERIAL ON % THROMBUS SURFACE AREA COVERAGE; (C) THE EFFECT OF MATERIAL ON ADHERED THROMBUS WEIGHT, NORMALIZED TO EACH TEST MATERIAL'S SURFACE AREA; AND (D) THE EFFECT OF MATERIAL ON THE REDUCTION OF PLATELET CONCENTRATION WITHIN THE BLOOD AFTER 1 HOUR OF CIRCULATION (PEBAX: N=5, ALL OTHER MATERIALS: N=6).

Computational fluid dynamic (CFD) simulation methods for predicting flow patterns and fluid stresses are increasingly being used in the development and premarket and post-market evaluation of blood-contacting medical devices. However, in order to rely on CFD-based predictions, the credibility of the simulations must be established through verification and validation. To develop and validate computational models of thrombosis and hemolysis in devices under clinically-relevant conditions, FDA has been working to bring together experimentalists and simulation experts to collaboratively establish models and credible data sets that may be used for CFD validation. Results from interlaboratory studies analyzing flow fields and hemolysis in two flow models (Fig. 3) can be found in our public data repository (https://ncihub.org/wiki/FDA_CFD) and have been used by other researchers to improve simulation practices [3].

To continue improving computational capabilities for designing and evaluating devices, FDA has partnered with medical industry experts through the Medical Device Innovation Consortium (https://mdic.org) to develop other experimental blood damage models and simulation modalities [4]. FDA recently presented a new method that combines CFD and a machine learning approach known as Gaussian process

regression with *in vitro* experimental data to calibrate empirical coefficients in a popular CFD hemolysis model [5]. This approach has the potential to significantly improve the predictive accuracy of CFD hemolysis modeling and may be readily extended to other models of flow-induced blood damage (e.g., platelet activation and thrombosis).

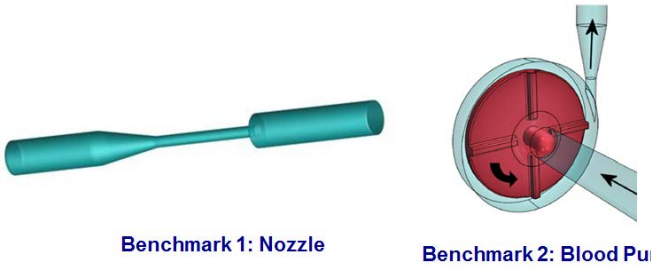

FIGURE 3: FDA FLOW MODELS USED IN INTERLABORATORY STUDIES.

2.2 Hemodynamics Research Group

The complex and highly variable nature of the cardiovascular system makes it difficult to accurately predict the flow behavior in and around medical devices. Device performance is often impacted by the surrounding environment, and thus, altered hemodynamics can lead to poor or adverse outcomes such as those described in the previous section associated with blood cell trauma. To mitigate device failure and reduce patient risk, it is critical to assess device-patient interactions under different pathophysiological conditions early in the total product life cycle using pre-clinical test methods with quantitative acceptance criteria. The test conditions should encompass the entire device operating range including extreme and worst-case operating conditions that may be relevant to a small subset of all the patients. Well-controlled, reproducible bench testing and computational simulations of flow and pressure fields have the potential to augment, or even replace, acute animal studies for characterizing the dynamic behavior of cardiovascular devices in a clinically-relevant environment prior to using them in patients. Currently, there is an overreliance on clinical data to assess the hemodynamic performance of cardiovascular devices due to a lack of credible pre-clinical test methods. Therefore, the primary aims of this research are to develop standardized pre-clinical test methods and regulatory tools including mock circulatory loops, particle image velocimetry (PIV) systems, and CFD models and establish hemodynamics performance acceptance criteria for accelerating patient access to high-quality, innovative, safe, and effective cardiovascular devices.

Current standard pre-clinical practices for characterizing the hemodynamic performance of cardiovascular devices are limited and not well-defined. For example, ventricular assist devices (VADs) are characterized by traditional pressure-flow curves in the absence of pathophysiologic conditions experienced by the device *in vivo*. To fully understand the flow through cardiovascular devices using least burdensome approaches, our group is developing new methods to assess the impact of multiple patient parameters and the sensitivity of device operating modes on flow performance [6, 7]. We are working with external stakeholders to identify and simulate various cardiovascular disease states (e.g., cardiogenic shock in Fig. 4) and establish consensus databases. Each cardiovascular flow model involves simulating fluid dynamic interactions among the device, blood, and the cardiovascular system (e.g., blood vessels, heart, heart valves, venous valves, and related fluid-structure interactions). The findings from this work help to determine achievable device operating ranges, circulatory support levels, and orientation of the device within the body, which will also inform the 'Instructions For Use' and product labeling.

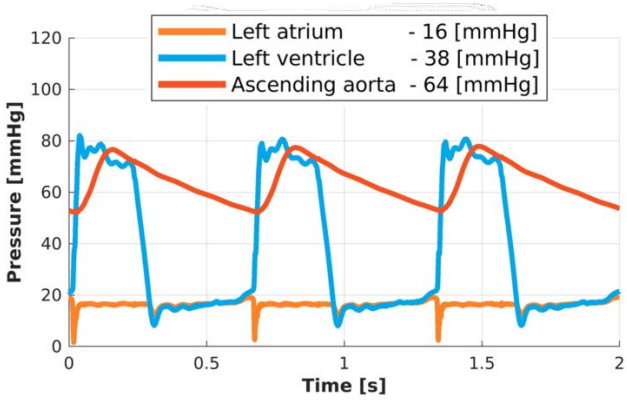

FIGURE 4: PATHOPHYSIOLOGICAL CONDITIONS, SUCH AS THIS CARDIOGENIC SHOCK WAVEFORM, CAN BE SIMULATED ON THE BENCH AND COMPUTATIONALLY TO STUDY DEVICE-PATIENT INTERACTIONS EARLIER IN THE TOTAL PRODUCT LIFE CYCLE.

To effectively evaluate emerging technological features of complex cardiovascular devices, new test protocols are needed and widely accepted standards are continually being revised (ISO 14708-5 and ISO 25539-3). For example, as more devices employ feedback control and adaptive capabilities, we are determining how to appropriately assess closed-loop control devices on the bench. VAD models are being developed to quantitate the impact of artificial pulsation, pulse synchronization, and the sensitivity of hemodynamic sensors. To bridge the gap between pre-clinical testing and clinical outcomes, we are establishing the credibility of, and validating, computational and *in vitro* models for cardiovascular device testing using real world data.

2.3 Device Durability Research Group

Given the importance of long-term durability to the safe and effective use of medical devices, our group has conducted research to investigate various aspects of durability. Multiple projects have been conducted to better understand corrosion and fatigue processes in metallic implants. Pre-clinical corrosion testing was often historically conducted on test specimens after they had been subjected to some kind of fatigue test with the notion that surface damage induced from the fatigue test might result in a lower and more realistic corrosion resistance value. The need to conduct corrosion testing after fatigue testing,

however, created logistical and technical problems for medical device manufacturers. Given these issues and since there had not been a systematic study of corrosion susceptibility before and after fatigue testing, our group conducted two studies to evaluate the effects of fatigue and fretting damage on corrosion susceptibility [8]. Overall, our findings suggested that any fretting or fatigue damage had minimal impact on corrosion susceptibility (Fig. 5). Therefore, FDA recommendations were updated to remove suggestions about conducting corrosion after fatigue testing which has simplified this aspect of pre-clinical durability evaluations (See FDA guidances "Select Updates For Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems" and "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol" at https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch).

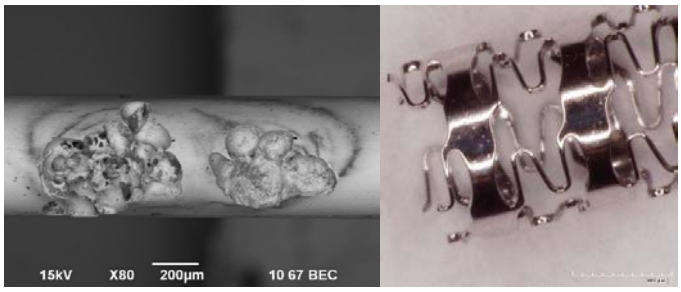

FIGURE 5: PITTING AND PLUME SEEN AFTER CORROSION TESTING IN A STAINLESS STEEL WIRE (LEFT) AND FRACTURED SURROGATE STENT-LIKE SPECIMEN (RIGHT).

For pre-clinical fatigue testing of cardiovascular devices like stents, endovascular grafts, etc., it is common to use computational modeling to select the size with the lowest fatigue safety factor for bench testing since it would be impractical to test every size. However, multiple methods of calculating fatigue safety factors exist and none had been validated against experimental data. In a recent study, our group partnered with industry to conduct a comprehensive study which evaluated different methods of calculating fatigue safety factors in a surrogate stent-like specimen [9]. In contrast to the commonly used scalar method, we found that the modified tensor method provided a more comprehensive approach for calculating mean and alternating stresses and their resulting fatigue safety factors.

Other research projects have focused more directly on specific finished medical devices such as heart valves. With the invention of transcatheter heart valves (THV) more than a decade ago, our group performed extensive experimental and computational research to evaluate how simulated non-circular configurations of the THVs may affect leaflet hydrodynamics and durability [10]. In line with least burdensome principles, the research adds more evidence to the importance of establishing a framework for each device design that may be helpful for picking the most challenging configurations for assessing acute hydrodynamic and chronic durability performance on the bench during device development.

Current efforts in device durability involve the evaluation of new experimental and computational techniques to improve fatigue testing by increasing confidence in the fatigue to fracture (FtF) methodology as described in ASTM F3211-17 standard. The FtF methodology, which is not being broadly used at present, may lead to a reduced pre-clinical test burden with shorter test times and safer devices along with a better understanding of loading conditions that lead to fracture. This work is being conducted in collaboration with industry partners and is simultaneously seeking to understand factors affecting ultra-high cycle nitinol fatigue life. Another project explores the use of credible computational modeling evidence combined with accelerated FtF testing of device surrogates to characterize the durability of a generic cardiovascular implant (Fig. 6) without testing full devices. Although historically the validation of implant solid mechanics modeling has been limited by the inability to directly measure primary quantities of interest for durability evaluation (i.e., stress, strain), full-field measurement techniques such as digital image correlation (DIC) are emerging as promising tools for characterizing device micromechanics, assessing model credibility, and improving model calibration and formulation. The overall objective of this project is to demonstrate the credibility of computational modeling in a real-world regulatory application following the risk-informed framework of ASME V&V 40 standard.

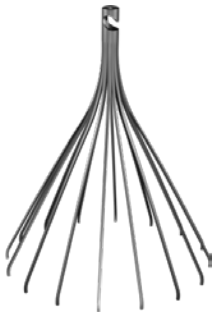

FIGURE 6: GENERIC MEDICAL DEVICE USED IN FDA RESEARCH

2.4 Electrophysiology Research Group

Preclinical *in vitro* and validated computational models need improvements to better understand performance of medical devices that monitor and affect electrical activity and contractility of the heart. The effect of electrical fields applied to the heart during the refractory period to treat heart failure patients (i.e., cardiac contractility modulation, or CCM) was studied using isolated rabbit cardiomyocytes and perfused whole rat hearts [11]. Single cell studies demonstrated an initial (only one beat) increase in intracellular calcium concentration and cell contraction, followed by a decrease to levels below control (before CCM). Whole heart studies revealed an increase on contraction in response to CCM, which was abolished in the presence of metoprolol, a beta-1 adrenergic blocker. The changes in intracellular calcium handling by cardiomyocytes did not explain the sustained positive inotropic effect in the whole heart and the b-adrenergic pathway may be involved in the action of CCM [11]. The study will be further extended to a human model,

using induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) [12].

iPSC-CM models are also used for ongoing research on cardiac ablation devices used to treat atrial fibrillation. Traditionally, thermal methods (radiofrequency, RF, heat or cryoablation, cold) are used to destroy pathogenic conduction pathways between pulmonary veins and the atria. Irreversible electroporation (IRE) by high intensity pulsed electric fields (PEF) is a new non-thermal modality to induce cell death that has not been approved for cardiac ablation. The focus of a new project is on the development of preclinical methods for the assessment of the safety and efficacy of IRE cardiac ablation devices. A systematic study is underway to quantify the *in vitro* effects of PEFs in human induced pluripotent stem cell-derived cells (both cardiac and non-cardiac) and verify in a large animal model through histological analysis of IRE-induced lesions. Electric field distribution maps are being obtained using numerical stimulation and the electroporation thresholds for both, cardiac (target) tissues and surrounding (off-target) tissues [13].

One integral component of cardiac electrophysiological research is computational modeling based on experimental data especially because clinical data, such as human action potential dynamics, are either scarce or limited by practical or ethical concerns. Whole heart models are being used clinically, for example, to stratify risk for implantable cardioverter defibrillators by predicting inducibility of ventricular arrhythmias. In [14], we report a "minimal" ionic model of the human action potential, based on *in vivo* human monophasic action potential recordings obtained during clinical programmed electrical stimulation to address the progressive increase in action potential take-off potential and associated conduction velocity slowing seen during three tightly spaced extra stimuli in patients. The new human cardiomyocyte model predicted the results of a clinical research study regarding the induction of arrhythmias via a combination of a measured intrinsic action potential duration heterogeneity. Computational modeling calibrated using clinical data provides a unique approach to study the initiation and maintenance of arrhythmias in humans *in vivo*.

Another important aspect of device design verification and validation testing is to design and develop novel preclinical methods that can predict clinical adverse events such as acute and chronic cardiac perforation of approved medical devices e.g. cardiac leads, in order to help improve and accelerate innovation for new safer medical devices. The simulation of physiologically relevant boundary conditions such as the addition of a right ventricular constraint during quasi-static buckling of different transvenous cardiac leads showed a substantial increase in the buckling mechanical loads at the distal tip [15]. These mechanical loads were imposed on a cardiac lead distal tip-tissue substitute under cyclic loading in a recent unpublished investigation to evaluate depth of penetration (Fig. 7) of different cardiac lead designs into the tissue substitute. The study preliminarily showed that penetration of different cardiac lead tip designs varied with some being more likely than others as the average maximum buckling load (AMBL) for each lead was increased by 25% and 50%; some leads appear to be more resistant to penetration into the tissue substitute than others. Amongst clinically existing variabilities such as patient anatomy (as represented by the two different tissue substitute gels as seen in Fig. 7) and implantation procedures, other device design factors e.g. outer lead diameter and the distal tip stiffness need to be considered during device design and development.

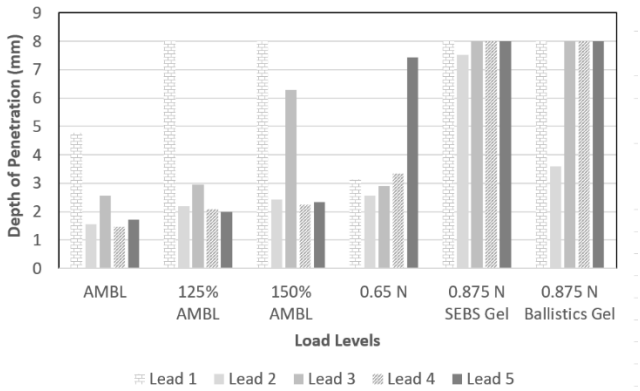

FIGURE 7: AVERAGE DEPTH THE DISTAL TIP OF 5 LEADS PENETRATED INTO THE TISSUE SUBSTITUTE AT VARIOUS LOADS (AMBL IS AVERAGE MAXIMUM BUCKLING LOAD; SEBS AND BALLISTICS GELS ARE DIFFERENT TYPES OF TISSUE SUBSTITUTES). THE MAXIMUM ALLOWABLE DISPLACEMENT WAS 8 mm IN THE TEST METHOD.

3. RESULTS AND DISCUSSION

The four research groups address regulatory gaps for evaluating the safety and performance of cardiovascular medical devices arising due to (1) a lack of standardized *in vitro* test methods, (2) a need for validated computational models and credibility assessments, and (3) insufficient correlations between *in vitro* and *in silico* results to real-world clinical performance. These regulatory gaps exist because of the variability in device designs and applications, difficulty in controlling test conditions and simulating patient conditions, and the need to improve computational models to better predict clinical outcomes early on and to make regulatory decision-making easier and consistent during pre- and post-market regulatory review process. To address these gaps the cardiovascular research program in OSEL continues to develop regulatory science tools (https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices) to help improve the assessment of emerging and existing medical device technologies.

4. CONCLUSION

The specific projects presented here help understand the motivation behind and offer a glimpse of the regulatory science research performed by OSEL's Cardiovascular Research Program. The research outputs from one regulatory science group can inform and overlap with research outputs of another group. The program is seeking feedback and collaboration with stakeholders to complete existing gaps, identify new gaps based on emerging devices, and expand our capabilities to have the most impact for the cardiovascular medical device community,

thus accelerating innovation and patient access to life-saving cardiovascular medical devices.

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