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IPR & Life Science News

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How to conduct Clinical Trials during the COVID-19 pandemic

The current crisis is making a major impact on clinical trials already ongoing as well as trials planned for the near future.

EU and national medicinal authorities have issued guidelines for sponsors, sites, and researchers on the management of clinical trials during the coronavirus crisis – but full harmonization of the rules has not been reached.

EU Guidance

On 20 March 2020, the EU Commission, together with the European Medicines Agency (EMA) and other stakeholders, issued a harmonized guidance "on the Management of Clinical Trials during the COVID-19 pandemic". This guidance has already been updated several times and a third version is now in place.

The guidance has been issued in response to the impact of the pandemic and the following emergency actions that require extraordinary measures for and adjustments of clinical trials. The limited access to healthcare facilities and staff, travel restrictions and self-isolated trial participants throughout the EU cause difficulties in conducting and completing clinical trials. The guidance is intended to minimize the negative effects on clinical trials caused by the COVID-19 pandemic by guiding involved parties and, temporarily, adjusting the ordinary regulation and guidelines on clinical trials.

The guidelines contain general information on risk assessment and ongoing safety reporting to relevant authorities, as well as specific changes and recommendations for new and ongoing trials.

Ongoing trials: Sponsors of ongoing trials are urged to consider the need for extending trial durations, closing sites, conducting critical laboratory tests as well as suspending or slowing down recruitment of new trial participants. It is further recommended that physical visits are postponed, cancelled, or converted into digital visits and sponsors must complete benefit/risk assessments for all trials.

New trials: Sponsors of new trials are asked to especially address the risk to possible trial participants. Further, the stakeholders behind the guidance are announcing their support for large, multinational trial protocols to investigate treatments for COVID-19, and if possible, through an accelerated Voluntary Harmonisation Procedure assessment. At this writing, more than 200 COVID-19 clinical trials are registered in the clinical trial database EudraCT.

Finally, the guidance emphasises that clinical trials are issued and supervised nationally. Therefore, there might be specific national legislation and guidelines to consult simultaneously.

National guidelines and harmonization challenges

While the purpose of the EU guidance is harmonization on EU/EEA-level, national guidelines may differ.

In Denmark, the Danish Medicines Agency (DMA) has issued a set of national guidelines on the management of clinical trials during the pandemic. The fifth version was published last week.

For Denmark, the most important clarifications and diversions from the EU guidance are:

1. **More lenient notification requirement**
   The DMA does not require notification on urgent safety measure implementations during the pandemic to the extent suggested in the EU guidance. However, notification of changes that do not comply with the Danish

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guidelines, and which will significantly impact the benefit-risk assessment of the trial, must be submitted instantly (within 7 days) in accordance with the EU guidance. Standard notification must be submitted once the situation is stable and future inspections will focus on processes implemented during COVID-19.

2. **Remote Source Data Verification allowed**
   In the EU guidance, the possibility of using remote source data verification (SDV) is extraordinarily allowed in trials related to COVID-19 and (other) life-threatening conditions. In previous versions, The Danish guidelines precluded such possibility in Denmark, but in the newest version, the DMA changed its opinion, now allowing remote SDV when verification is needed to ensure the quality of the final data and when a monitoring plan is prepared. In this regard, the DMA stresses that remote SDV should only be required in very few clinical trials that are investigating treatment and prevention of COVID-19 and pivotal clinical trials soon reaching trial completion.

3. **Direct distribution of IMPs from sponsor to participant**
   The Danish guidelines allow investigational medicinal products (IMP) to be dispatched from sponsor directly to trial participants under certain conditions. This is also possible under the EU guidance. The Danish rule is, nonetheless, a provisional exemption from the general rule requiring dispensing of IMPs through a doctor. Both the distribution-exemption and the above-mentioned lenient notification requirement are valid until 1 September 2020 (and are extendable with a two-week notice.

Like Denmark, most other EU Member States have issued guidelines for clinical trials during the pandemic deviating from the EU guidance. Thus, complete harmonization with the EU guidance is clearly lacking. For instance, guidelines in some countries differ from the Danish guidelines on allowing direct distribution of IMPs from sponsor to participants. Also, the notification requirement varies greatly in the national guidelines, and while changing positions in national guidelines (such as the Danish shift to allowing remote SDV) might ensure flexibility, they pose a great challenge for sponsors conducting clinical trials, as they and other stakeholders are forced to navigate in an unharmonized, constantly changing regulatory landscape.

While such discrepancies might call for wider EU harmonisation, it may prove difficult to carry into effect considering EU's lack of legislative power on healthcare issues. Ultimately, member states and not the EU have the authority to approve and oversee clinical trials.

Both the EU Guidance and Danish Medicines Agency Guidelines are being updated on an ongoing basis and are, as of right now, in its respectively third (28/04/2020) and fifth version (25/04/2020).

Accura's dedicated team of IP & Life Science experts follows the development of the guidelines closely.

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The advocate general challenges recent CJEU case law on SPCs for second medical use

With the Advocate General Opinion in Santen (C-673/18), the Court of Justice of the European Union (CJEU) is called upon to clarify the scope of Neurim (C-130/11); the highly influential decision that opened the possibilities for the grant of SPCs for second and further medical uses.

In the wake of the decision in Neurim, several different interpretations of Neurim emerged and the judgement became the subject of wide discussion due to it seemingly being in direct conflict with the wording of regulation 469/2009 (the SPC regulation). With the Santen case (C-673/18) the CJEU will soon address how the concept of a 'different application' within the meaning of Neurim must be understood.

Current legal landscape

The position of the CJEU in relation to SPCs for second and further medical uses has undergone a rather turbulent development. The issue in a nutshell regards the substance of the word 'product', since the SPC regulation provides that a given marketing authorization (MA) must be the first to place the 'product' on the market according to the SPC regulation Art. 3(d).

In Pharmacia C-31/03, the CJEU held that the decisive factor for the grant of the certificate is not the intended *use* of a medicinal product. The facts were:

First MA	Second MA
Veterinary use Indication A	Human use Indication A

In Yissum C-202/05, it was held that if a basic patent protects a second medical use, this is not an integral part of the definition of 'product'. The facts of the case were:

First MA	Second MA
Human use Indication A	Human use Indication B

Yissum concerned the definition of 'product' in the SPC regulation Art. 1(b) and upheld an established narrow interpretation of the provision. It is relevant in relation to Art. 3(d) since it would seem that if a therapeutic use is immaterial for determining whether something is a 'product' within the meaning of Art. 1(b), it suggests that it must also be immaterial for determining whether a given MA is the first to place the 'product' on the market according to Art. 3(d).

Along came Neurim C-130/11 which concerned both different species *and* different indications:

First MA	Second MA
Veterinary use Indication A	Human use Indication B

The court, before which the case first was brought, namely the High Court of England, found that since a difference in species *or* indication had been considered immaterial in Yissum, a difference in species *and* indication could by inference be considered immaterial as well. However, the British Court of Appeal considered Neurim's arguments in support of its claim for a second medical use SPC to be right, and if the SPC regulation was to be interpreted as to disallow second medical use SPCs it would render the regulation unfit for its purpose. Considering the stakes, the British Court of Appeal referred the matter to the CJEU.

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In its judgement, the CJEU considered that a fundamental objective of the SPC regulation is to ensure sufficient protection to encourage research, including such research into known active ingredients as that conducted by Neurim. Hence, the CJEU adopted a broad interpretation of 'product' in relation to Art. 3(d), allowing for the grant of an SPC for a different application of the same 'product' for which an MA has been granted.

However, in the Abraxis C-443/17 decision the CJEU attempted to align itself with the case law prior to Neurim once again. The facts of Abraxis were:

First MA	Second MA
Human use Indication A Formulation A	Human use Indication A Formulation B

In the case, the CJEU confirmed the established strict interpretation of Art. 1(b) and re-established a connection between this provision and Art. 3(d). Despite the Neurim holding being difficult to reconcile with the prior case law, the CJEU refrained from rescinding Neurim. Instead, the CJEU chose to classify it as a narrow exception to the strict interpretation, being applicable only to specific factual scenarios like that in Neurim.

The preferred Opinion of the Advocate General in Santen

In Santen C-673/18, the Advocate General (AG) advises the CJEU to follow a strict interpretation as in Abraxis, while departing from this judgement in suggesting that the CJEU expressly abandon the Neurim holding. This is advised since, to his mind, Neurim cannot be read as a narrow exception to the strict interpretation as held in Abraxis.

The AG finds that neither a literal, schematic nor teleological interpretation can lead to Neurim being an applicable authority on the matter. It is clear from the opinion that the AG considers it inappropriate to stretch a teleological reasoning too far, especially in the highly technical and complex pharmaceutical sector where delicate choices of economic and social policy is involved. The AG fears that following Neurim will introduce new uncertainties and shift the balance of interests in favor of originator companies. For these reasons, the AG calls upon the CJEU to resolve the systemic inconsistencies in the case law.

Opinion in the alternative

In the event that the CJEU does not agree with the above, the AG proposes that the CJEU adopts an intermediate approach between the two extremes; the strict interpretation only applying to the specific factual scenario (prior MA for veterinary use) and the broad interpretation, namely to include different formulations, dosages, methods of administration etc. This intermediate approach should cover two cases: Firstly the case of a new therapeutic indication, making it possible to treat new diseases, and secondly the case where the old active ingredient exerts a pharmaceutical effect of its own, different from that previously known. This approach applies a threshold that will e.g. not be met in the case of new formulation of an old active ingredient that consists of the addition of a carrier that does not have a pharmaceutical effect on its own.

The AG further suggests, that where an SPC relates to a different application, the term 'product' as used in Art. 4, which determines the scope of protection of an SPC, must be interpreted as only referring to that application and thus not extending to the active ingredient as such.

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Accura comments

The opinion of the AG is a welcome contribution to an area of the law characterized by a high degree of legal uncertainty, which could benefit from more comprehensive judgements from the CJEU.

In the preferred suggested option, the AG applies a strict interpretation with the outcome that the possibilities for obtaining second medical use SPCs are significantly limited. The argument that a party undertaking prolonged and expensive research in order to identify second and further medical uses should be able to secure a fair compensation via the SPC regime may be easy to endorse. However, so is the argument that the Neurim judgement lacks sufficient legal legitimacy as it can be considered to go against the wording of the SPC regulation, established case law and many elements from the proposal for the SPC regulation (i.e. the Explanatory Memorandum).

Of interest is that the AG suggests an intermediate approach as an alternative, as in particular the comprehensive *"Study on the Legal Aspects of Supplementary Protection Certificates in the EU"* by the Max Planck Institute expressly holds that such an approach is *prima facie* not justified without indication of the time and investment needed to bring a new formulation on the market being different compared to that for a new indication. Furthermore, the study suggests that such an intermediate approach would risk overburdening the national patent offices.

The opinion of the AG is a very valuable read, as it proposes two options for the CJEU sharing the common feature that an adoption of either would provide a higher degree of legal certainty in an area of the law that has been lacking in this regard for years.

Danish High Court dismisses illegal downloading and file sharing cases

The Danish Eastern High Court recently dismissed three appeal court cases on illegal downloading and file sharing due to the plaintiff's lack of standing to pursue the claims on behalf of the copyright holders.

The rulings are a gamechanger for rightsholders and accused internet subscribers and have already led to numerous case dismissals by the district courts.

Several hundred cases of alleged illegal downloading and filesharing recently took a turn when three appeal court cases were dismissed by the Eastern High Court. The precedent in the majority of these cases has been based on a rule of presumption after which the violation must be presumed to be committed by the owner of the IP-address, if he or she had an access code on their internet connection. Read more about the preceding court cases and the rule of presumption in our previous newsletter *(open here)*.

Whilst the Eastern High Court does not set aside the rule of presumption, the court ruled that the plaintiffs lacked standing to pursue the copyright holders' claims, which led to the High Court revoking and dismissing all three court cases. The High Court rulings are likely to have immense consequences for several hundred similar district court cases, which have been put on hold while awaiting the appeal rulings. 39 cases in the District Court of Frederiksberg have already been dismissed.

The High Court's dismissals

The three court cases were all appealed and processed together before the Eastern High Court. As argued in many similar previous court cases, the defendants claimed that the plaintiff lacked standing to pursue the matter due to the licensing agreements presented being inadequate and imprecise. The plaintiff, a British registered company acting on behalf of the copyright holders, claimed affirmation of the district court rulings by arguing that the company by virtue of the licensing agreements had acquired the necessary standing to sue. Despite the many previous district court rulings, the Eastern High Court found that the licensing agreements were in fact inadequate. Furthermore, the plaintiff had neither produced nor distributed the movies concerned and was therefore not the rightful owner of the copyrights and the associated standing to sue. The license agreements between the plaintiff and a Cypriot company, who had been assigned copyrights from an American film producer, did not prove that the rights had been assigned to the plaintiff. The license agreements were only partially submitted as evidence in the case and the plaintiff was mentioned by its previous name, which had been changed prior to the license agreement. Finally, an e-mail from the alleged director of the Cypriot company stating that the rights had in fact been assigned to the plaintiff did not change the High Court's rulings.

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Pending district court cases are being dismissed

With the dismissals from the Eastern High Court, the district courts have now commenced to process the numerous cases that have been put on hold. In the District Court of Frederiksberg alone, 39 cases out of a caseload of 150, have been dismissed on the grounds that the plaintiff is lacking standing to sue.

In the dismissals, the District Court of Frederiksberg further elaborates on the arguments that have long been conveyed by defendants' counsel, including numerous issues with the evidence in these types of cases, such as problems with the technical documentation and the plaintiff's management of such evidence towards individuals with no legal background or knowledge. Another issue pointed out by the district court, is the plaintiffs' inactivity meaning that most claims are presented several years after the accused illegal actions. Moreover, the district court finds that the plaintiffs seek overcompensation both in trial and in settlements.

The cases of illegal downloading and file sharing might not be over just yet, as the plaintiff's counsel has recently stated that the plaintiff might appeal the three cases to the Danish Supreme Court.

Accura's team of IP specialists follow the matter and developments closely.

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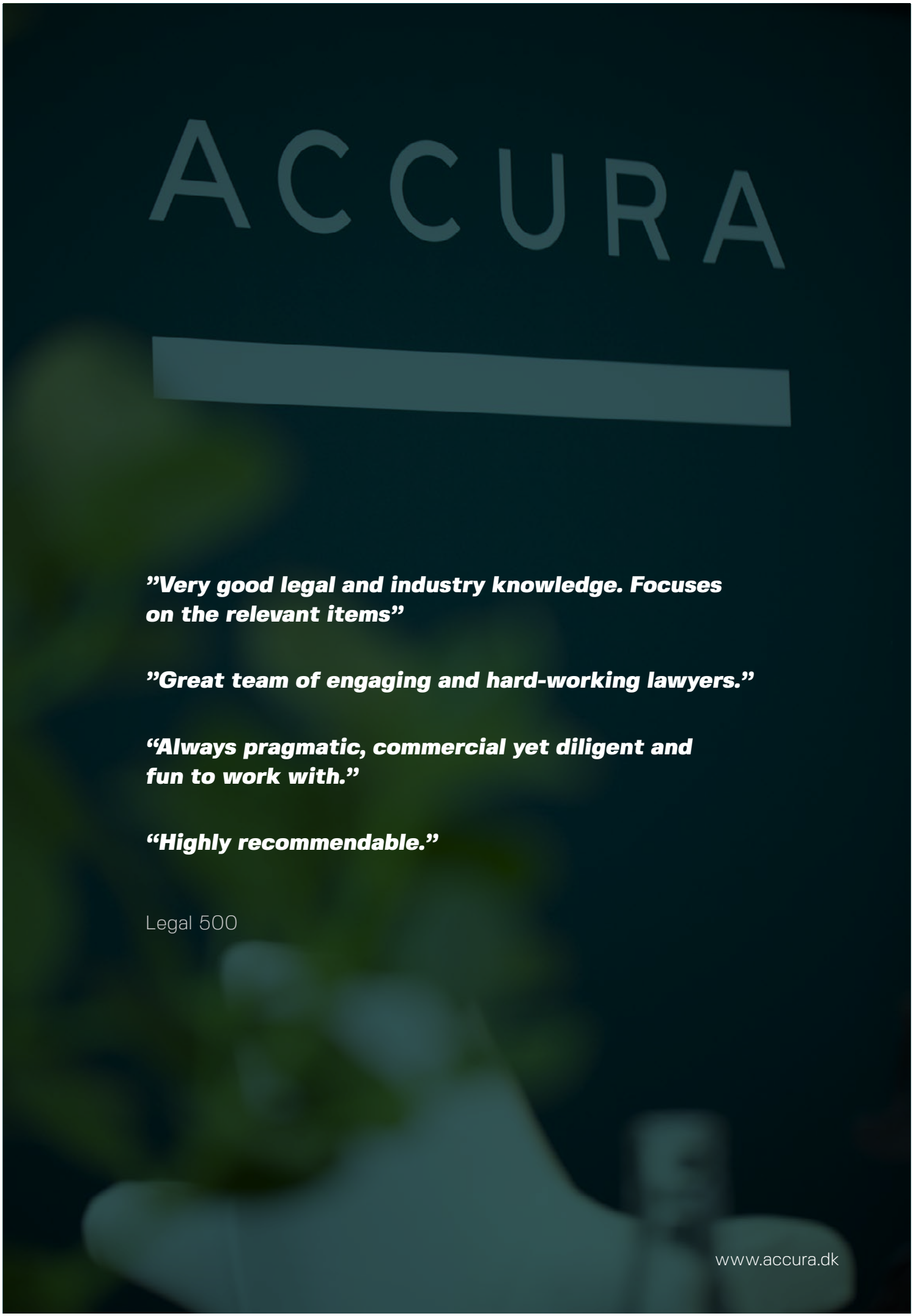

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