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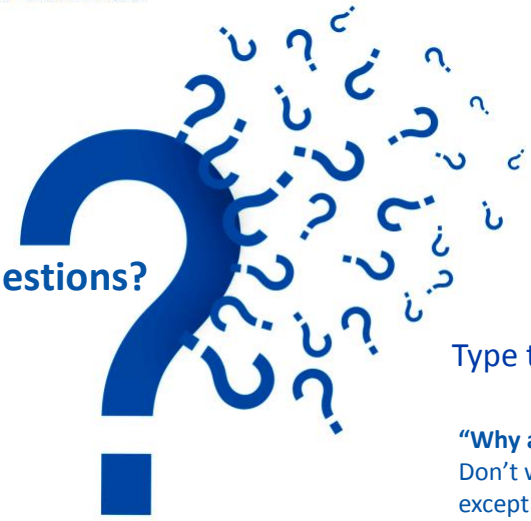

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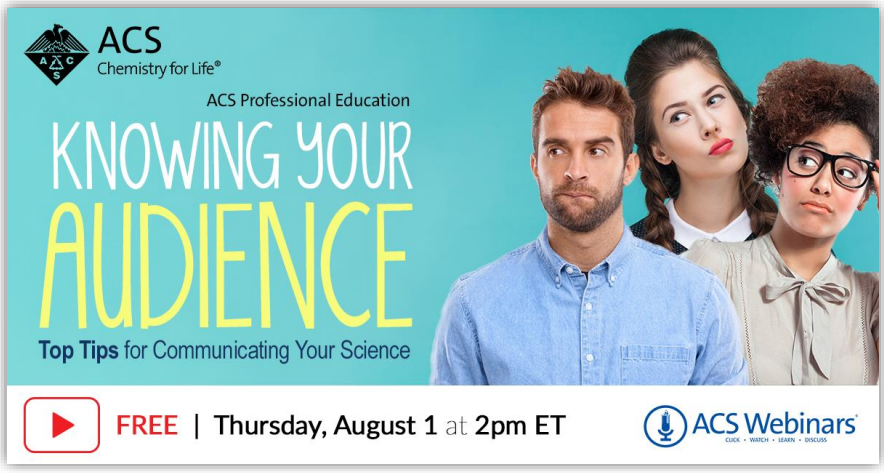

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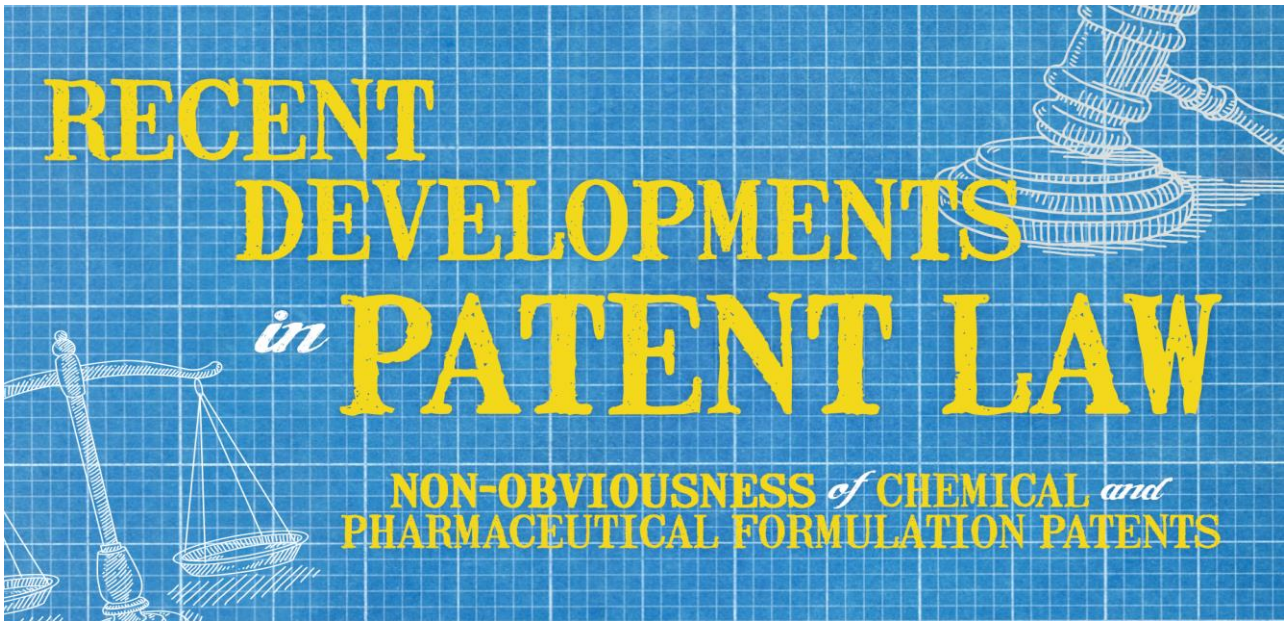

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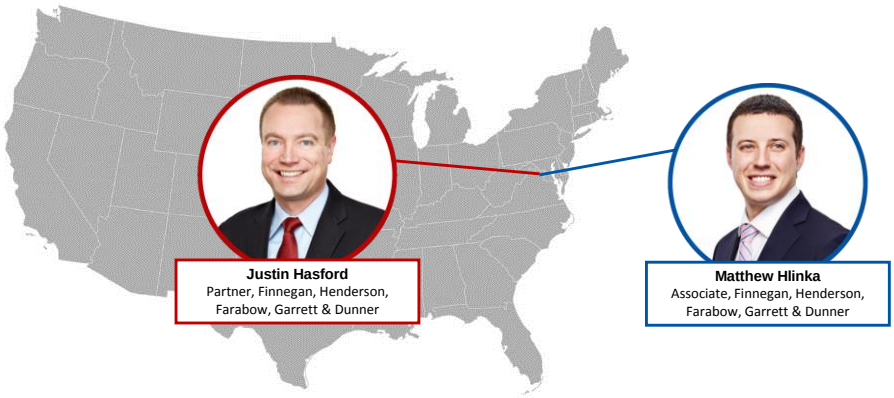
Recent Developments in Patent Law: Non-Obviousness of Chemical and Pharmaceutical Formulation Patents



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Finnegan, Henderson, Farabow, Garrett & Dunner, LLP

Recent Developments in Patent Law: Non-Obviousness of Pharmaceutical Formulations

July 18, 2019

Presented by Justin J. Hasford

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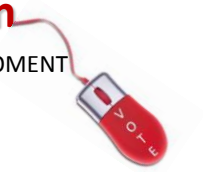


In its **1966 Graham v. John Deere Co.** decision, the U.S. Supreme Court established a methodology for making a judgement when a patent's non-obviousness is challenged. **There must be an assessment of which of the following:** (more than one possible answer may exist)

- The differences between the prior art and challenged claims
- The level of ordinary skill in the field of the pertinent art at the time of the plaintiff's invention
- The scope and content of the prior art
- The manner in which the invention was made
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

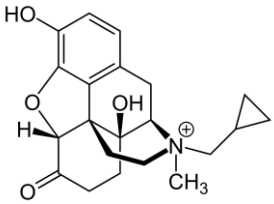
Valeant v. Mylan & Actavis, 15-cv-8180 (D.N.J.)

- Hatch-Waxman case involving Mylan's and Actavis' attempts to market generic copies of Relistor® subcutaneous

- Assigned to Judge Stanley Chesler in Newark
- **Won summary judgement of non-obviousness**
  - Judge Chesler found no genuine factual issue warranting trial on Mylan's and Actavis' obviousness defense

U.S. Patent No. 8,552,025

- Covers Relistor® subcutaneous
- Directed generally to stable pharmaceutical preparations comprising solutions of **methylnaltrexone** ("MNTX")
- Mylan and Actavis stipulated to infringement of claims 8, 20, and 23
- Defendants' only remaining argument: **invalidity based on alleged obviousness**



The '025 Patent

- **Claim 8** (in independent form):

  A stable pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation comprises a pH between about 3.0 and about 4.0, wherein the preparation is stable to storage for 24 months at about room temperature.

- *"It was surprisingly discovered that pH alone can solve the problem of excessive methylnaltrexone degradation products."* Col. 8, ll. 47-49.

Defendants' Arguments

Defendants' alleged obviousness references:

- **Methylnaltrexone references:**
  - **Foss 2001:** clinical use of MNTX in opioid bowel dysfunction; no mention of solutions of MNTX or storage/degradation thereof
  - **Foss '954:** routes of administration of MNTX; describes clinical study of IV administration of saline solution of MNTX
    - No mention of storage stability or degradation issues
- **Naloxone/naltrexone references:**
  - **Bahal '154:** naloxone only; no 24 month storage stability
  - **Oshlack '111:** naltrexone; no 24 month storage stability
- **General pharmaceutical formulation references:**
  - **Gibson:** no mention of MNTX; no 24 month storage stability
  - **Remington:** no mention of MNTX; no 24 month storage stability

Defendants' Arguments

Defendants argued it allegedly would have been *"obvious to try"* the claimed pH range and achieve the claimed stability

- Defendants argued *"about 3 to about 4"* falls within pH ranges in the art for naloxone and naltrexone = *prima facie* obvious
- Defendants argued that adjusting pH would be the *first* variable to improve stability considered by a person of ordinary skill in the art
- Defendants argued that a skilled artisan would expect the pH ranges allegedly disclosed as stabilizing naloxone and naltrexone to work for MNTX and result in 24-month storage stability at room temperature

Defendants' Failures of Proof on Claim 8

In contentions, expert reports, and expert depositions:

- No identified stability problem with saline solutions of MNTX
- No reference teaching 24-month storage stability at room temperature
- No reference teaching a pH of about 3 to about 4 as stabilizing any compound, much less MNTX, and certainly not for 24 months at room temperature

Summary Judgement Standard

Summary judgment is appropriate when the moving party demonstrates that there is no genuine issue of material fact, and the evidence establishes the moving party's entitlement to judgment as a matter of law. *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986)

- **Genuine** factual dispute = if a reasonable fact finder could return a verdict for the non-movant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986)
- **Material** fact = under the substantive law, it might affect the outcome of the suit. *Id.*

Holding

Judge Chesler granted summary judgment of validity of claim 8

- Persuaded that *"Defendants cannot prove their 'obvious to try' theory"*
- *"The heart of Defendants' obviousness case−and the major point on which they fail−is their argument that a pH range of 3 to 4 would have been obvious to try. . . . The bottom line is that Defendants have pointed to no evidence that claim 8 was either an 'identified, predictable solution' or an 'anticipated success.'"*

See 15-cv-08180, ECF No. 300 at pp. 3, 4, 6.

Defendants' Argument re "Overlapping Ranges"

Defendants first argue that the pH range is *prima facie* obvious in view of allegedly overlapping ranges in Bahal '154, Oshlack '111, and Fawcett 1997

Judge Chesler disagreed:

- *"Not one of the three cited pieces of prior art teaches the use of methylnaltrexone in any form."*
- *"Defendants have here presented no evidence that the claimed invention−a methylnaltrexone solution−can be said to fall within the pH ranges for naloxone or naltrexone solutions in the prior art."*
- *"[F]or the principle of overlapping ranges to apply, the difference between the claimed invention and the prior at must be the range or value of a particular variable."*

See 15-cv-08180, ECF No. 300 at pp. 7,8.

Cases Cited by the Court: Overlapping Ranges

Haynes Int'l, Inc. v. Jessop Steel Co., 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993)

- *"[W]hen the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in range or value is minor."*

See 15-cv-08180, ECF No. 300 at p. 8.

Defendants' Argument re "Finite Options"

Defendants argue that a pH of 3 to 4 was just one of a finite number of options of pH ranges falling between 3 and 7

Judge Chesler:

- *"This is simply false: given any two unequal numbers, the quantity of number ranges falling between the two is infinite, not finite. This is basic math."*

See 15-cv-08180, ECF No. 300 at p. 9.

Defendants' Argument re "Obvious to Try" pH

Defendants argue that pH is the first or primary variable a formulator would consider for stability

Judge Chesler disagreed:

- *"Defendants seem to suggest that adjusting pH was the leading option, but no evidence supports this."*
- *Reviewed Defs.' cited evidence in detail, concluding none supports their assertion and some is "misleading"*
- *"It is undisputed that a skilled artisan, faced with the problem of formulating a stable injectable methylnaltrexone solution, would have at least six options to consider: pH, stabilizers, antioxidants, chelating agents, container closure system, and preservatives."*

See 15-cv-08180, ECF No. 300 at pp. 9-11.

Testimony of Dr. Khan, Defendants' Expert

- Judge Chesler cited from the deposition of Defendants' expert Dr. Khan:

Q: It is your opinion that one of ordinary skill in the art would have expected pH to be one of the leading candidates for resolving stability issues along with excipients, such as stabilizers, antioxidants, and kelating agents, correct?

A: Correct.

- *"The point here is that, in the cited testimony, Dr. Khan did not identify adjusting pH as the primary approach to adjusting formulation stability. Instead, he placed it in a group of leading approaches with a number of other members."*

15-cv-08180, ECF No. 300 at pp. 10-11.

Teachings of the Art

Judge Chesler found that the art taught many options, based on Defendants' expert's own testimony:

- *"Defendants' evidence indicates that the skilled artisan, seeking to develop a methylnaltrexone injectable solution with long-term stability, 'would have had to try all possibilities in a field unreduced by direction of the prior art.'"*
- *"[F]or claim 8, Defendants have shown only that the skilled artisan would have recognized adjusting pH as one dart among a number of others."*

Cases Cited by the Court: Hindsight

Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008)

- *"In the absence of evidence that optimizing pH was the leading option for improving stability, as Plaintiffs contend, Defendants have 'retraced the path of the inventor with hindsight.'"*

Defendants' Argument re "Predictable Result"

Defendants argue that arriving at claimed pH range for long-term MNTX stability "a predictable result"

Judge Chesler disagreed:

- *"Dr. Khan's conclusion does not go farther than to say that the skilled artisan would have expected that formulations of [MNTX] with an acidic pH would have unspecified stability. There is a large gap between this expected result and claim 8 . . ."*

See 15-cv-08180, ECF No. 300 at pp. 11-12.

Defendants' Arguments re Naloxone/Naltrexone

Defendants argue that a skilled artisan would have used the pH range for naloxone/naltrexone and expected similar stability for MNTX

Judge Chesler disagreed:

- *"Bahal '154 does not discuss at any point the role of pH in stability" and "Oshlack '111 does not at any point disclose the use of pH alone to stabilize naltrexone solutions"*
- *"This is a crucial underlying factual proposition for Defendants' obviousness case, and Defendants have failed to offer evidence from which a reasonable jury could find this to be true."*

See 15-cv-08180, ECF No. 300 at pp. 13-15.

Defendants' Impermissible Use of Hindsight

Defendants' failure to identify the 24-month storage stability element in the prior art is problematic for their **"obvious to try"** argument:

- *"[I]t bears repeating that, based on the evidence of record, the prior art did not teach injectable pharmaceutical solutions with 24-month stability. Thus, for the invention of claim 8 to have been contemplated as a predictable result, there must be evidence of a basis to predict something that had never been accomplished before could be accomplished. In the absence of such evidence, calling claim 8 a predictable result shows the operation of hindsight"*

See 15-cv-08180, ECF No. 300 at p. 15.

Defendants' Failure on Reasonable Expectation of Success

Defendants argue that a skilled artisan would have a reasonable expectation of success achieving 24 month storage stability at room temperature

Judge Chesler disagreed:

- *"The bottom line is that this section of Defendants' brief points to no evidence supporting an inference that claim 8 was a predictable result or that a skilled artisan, looking at the prior art, would have reasonable expected success with the formulation in claim 8."*
- Defendants' reliance on Bahal '154 is flawed, regardless of whether compounds are structurally similar, because it teaches the use of stabilizers such as sodium edetate to stabilize naloxone, not pH alone.
  - "*Dr. Khan's statements about Bahal '154 . . . are 'conclusory statements [which] do not raise any genuine issues of material fact.'"*

See 15-cv-08180, ECF No. 300 at pp. 15-17.

Testimony of Dr. Hunter, Defendants' Expert

- Judge Chesler cited from deposition of Defendants' expert Dr. Hunter:

Q: But does Bahal ever attribute the stabilization of naloxone to the adjustment of pH to 3.2?

A: Bahal is silent on the effect of pH on the stability of naloxone.

  - *"Dr. Hunter, Defendants' chemistry expert, supported th[e] inference in his deposition testimony" that Bahal '154 "appears to teach that naloxone saline solutions at pH 3.2, without an added stabilizer, fail the stability test. . . ."*

Cases Cited by the Court: Conclusory Testimony

ActiveVideo Networks, Inc. v. Verizon Communs., Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012)

  - *"Rather, the expert's testimony on obviousness was essentially a conclusory statement that a person of ordinary skill in the art would have known . . . how to combine any of a number of references to achieve the claimed inventions. This is not sufficient and is fraught with hindsight bias."*

  - Judge Chesler stated *"[t]hat is true of Dr. Khan's cited testimony, as well."*

Court: Not "Obvious to Try"

"The evidence of record, viewed in the light most favorable to the non-movants, supports the inference that, at the time of the invention, the skilled artisan would have expected that the stability of methylnaltrexone solutions might be improved both by making the pH acidic, and by optimizing that acidic pH for peak stability. That does not provide a sufficient factual basis for a finding that, to the skilled artisan, the invention of claim 8 would have been a predictable result. There is still a substantial logical gap between that knowledge and the discovery that methylnaltrexone solutions are stable for 24 months when the pH is adjusted to the range of 3 to 4 without the use of other stabilizers. Defendants have pointed to no evidence that supports the inference that the skilled artisan had any basis to predict that that specific pH range would be associated with stability of that duration."

FINNEGAN 15-cv-08180, ECF No. 300 at p. 19. 37

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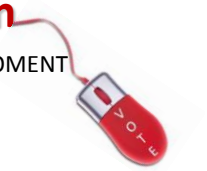

In the **2007 KSR Int'l. Co. v. Teleflex Inc.** ruling, the Supreme Court added a fourth potential factor: objective, or "secondary," considerations when a patent's non-obviousness is challenged**.** **These may include:** (more than one possible answer may exist)

- The commercial success of the invention
- Whether the invention satisfies a long-felt need in the industry
- Failure of others to find a solution to the problem the invention solves
- Copying or licensing by others
- Experts' praise or skepticism regarding invention

** If your answer differs greatly from the choices above tell us in the chat!*

Cases Cited by the Court: "Obvious to Try"

Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009)

- *"[A]n invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art."*
- *"[A]n invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution"*
  - Judge Chesler stated these quotes "express[] well the reasons why Defendants have failed to defeat Plaintiffs' motion for partial summary judgment."

Endo v. Custopharm, 894 F.3d 1374 (Fed. Cir. 2018)

- Hatch-Waxman case involving Custopharm's attempt to market generic copy of Aveed® testosterone undecanoate ("TU") injection

- Endo owns '640 and '395 patents covering Aveed®
  - Claims directed to TU compositions with (a) 750 mg TU; (b) a vehicle containing 40% castor oil and 60% benzyl benzoate co-solvent ('640 patent only) and (c) an injection schedule comprising two initial injections at an interval of four weeks followed by injections at ten week intervals ('395 patent only)

Custopharm Argued Inherent Obviousness

- **Custopharm asserted the Behre, Nieschlag and von Eckardstein clinical study references**
  - All involve administering 1000 mg TU in castor oil
  - None discloses or describes a 40% castor oil / 60% benzyl benzoate vehicle
    - While this was actually used in the clinical study formulations, this was unknown to a person of ordinary skill in the art until long after the priority date of Endo's '640 and '395 patents
- **Custopharm also asserted the Saad reference**
  - Not prior art; published four years after priority date
  - Discloses that the Behre, Nieschlag and von Eckardstein clinical study formulations used a 40% castor oil / 60% benzyl benzoate vehicle

No Inherent Obviousness

- District Court rejected Custopharm's inherent obviousness argument, and Fed. Circuit affirmed
- *Par v. TWI*: inherency requires that *"the limitation at issue necessarily must be present, or [is] the natural result of the combination of elements explicitly disclosed by the prior art."*
- Later revelation of the limitation does not mean that it necessarily must be present in the prior art
- Here, the pharmacokinetic profiles in the clinical references did not necessarily point to use of the claimed vehicle or bar the possibility of alternatives

Court Rejected Custopharm's Dose Arguments

- Custopharm argued that 1000 mg TU was an overdose, thus motivating a 750 mg TU dose
- Custopharm relied on AACE guidelines, but under FDA guidelines no subject received overdose
- Custopharm could not show motivation in prior art to lower dose, especially in light of FDA guidelines
- Even if Custopharm's overdose argument were correct, injection intervals could be extended without lowering the TU dose

Court Rejected Motivation-to-Combine Argument

- Custopharm relied on Prolution, an injectable steroid in a 40% castor oil / 60% benzyl benzoate vehicle
- But Prolution is not a testosterone product for men; rather, it is administered to pregnant women to prevent miscarriage
- Importantly, unlike the claimed formulations of the '640 and '395 patents, Prolution is not an injectable steroid with prolonged activity

Court Rejected Injection Schedule Arguments

- Custopharm argued that the claimed injection schedule would be routine and thus obvious
- But this argument was predicated on the overdose argument that the Court rejected
- Importantly, the clinical study prior art did not teach initial loading doses followed by maintenance doses
- Endo presented evidence that dosing of TU injections is unpredictable and requires more than routine experimentation

Our Presenter

Justin J. Hasford is a partner in Finnegan's Washington, D.C. office

Justin Hasford's practice focuses on complex litigation at the trial and appellate levels, as well as pre-litigation due diligence, on behalf of pioneer pharmaceutical and chemical companies. Justin has particular experience in cases arising from Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act. Justin also has litigated antitrust and business method patent cases.

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Our Moderator

Matthew J. Hlinka is an associate in Finnegan's Washington, D.C. office

Matthew Hlinka focuses on patent and trade secret litigation before U.S. District Courts, primarily in the areas of pharmaceuticals and chemical products. He also represents clients in international arbitrations. He has represented several branded pharmaceutical companies in Abbreviated New Drug Applications (ANDA) litigations under the Hatch-Waxman Act and in international arbitrations.

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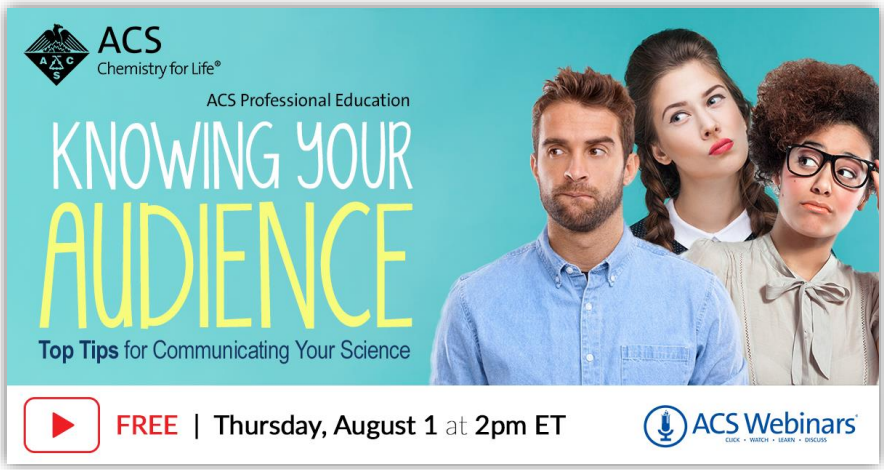

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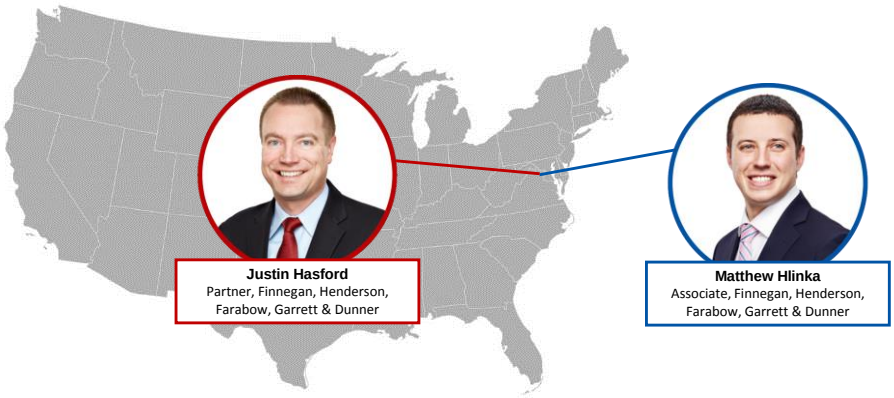

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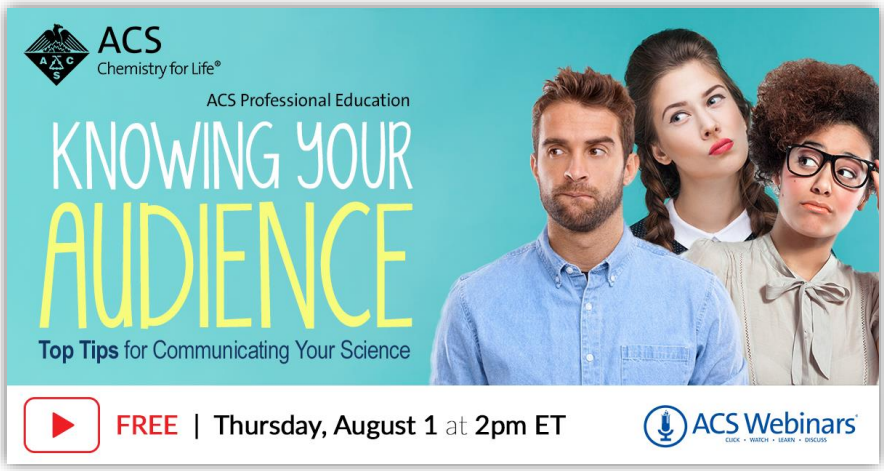

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